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Rieser, Willy and Rieser, S. L.: The etiology of orthostatic albuminuria. J. Am. M. Ass., 1922, *78*, 644.

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THE ORIGIN OF THE WORD PROTEIN*

HUBERT BRADFORD VICKERY

The word protein first appeared in scientific literature in 1838. It was used by Mulder as the designation of the complex radical which he thought to be combined with sulfur and phosphorus in the proteins as they occur in nature, and it has been commonly assumed that he himself originated the new term. That this is incorrect has recently been pointed out by Sir Harold Hartley[1, 2] who, in the course of preparing an address commemorating the centenary of the death of Berzelius, found that Berzelius had suggested the word protein to Mulder in a letter written from Stockholm on July 10, 1838.[3]

Inasmuch as the correct origin of this word has been almost universally overlooked, the sequence of events which led to its publication may be of interest.

Mulder's investigations of proteins were begun in 1835 with chemical analyses of silk[4] and were soon extended to include fibrin, serum and egg albumin, gelatin, and a preparation of what is today known as wheat glutenin, together with various products derived from these substances by the action of acids and alkalies. Certain apparent regularities in the ultimate composition of the preparations convinced him of the presence in each of them of what contemporary chemical theory regarded as an oxidized basic radical which combined in simple ratios with sulfur and phosphorus to give the substances as they are found in nature. The name "protein," derived from the Greek adjective πρωτεῖος, meaning of the first rank or position, was given to this radical.

Mulder was convinced of the importance of these results and took what today seem rather extreme steps to provide for their wide dissemination. Two papers were published in journals of which he was himself an editor. In one of these, *Natuur- en scheikundig Archief*, his account[5] appears in volume 6 under the title "Over Proteine en hare Verbindingen en Ontledingsproducten" and runs from pages 87 to 162. A briefer article was

* From the Biochemical Laboratory of the Connecticut Agricultural Experiment Station, New Haven, Conn. The writer is most grateful to Professor A. C. Chibnall, who drew his attention in June 1949 to the address by Sir Harold Hartley given the previous September in Stockholm, and especially to Sir Harold Hartley for additional information and for his gracious assent to the publication of the present note.

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printed in the recently established semi-monthly *Bulletin des sciences physiques et naturelles en Néerlande* where it is to be found in the issue dated July 30, 1838, in volume 1, page 104, under the title "Sur le composition de quelques substances animales." *[6]

Mulder also wrote a letter to Liebig† giving an outline of his analytical results and views, and the substance of this letter, with the notation *"aus einem Briefe an J.L.,"* was published in *Annalen,* volume 28, page 73, in 1838.[7] In addition, the *Bulletin* paper was reprinted in German translation in the *Journal für praktische Chemie,* volume 16, pages 129 to 152, in 1839.[8]

In each of these papers, a statement is given of the derivation of the term protein. The sentence in the *Archief* paper may be roughly translated, "When all that has been described above is considered, it is clear that there is present in plant albumin,‡ and in the animal albumin of silk, of eggs, of blood serum, as well as in blood fibrin, a substance common to all that we designate *protein* from *πρωτεῖος, primarius,* which is combined with sulfur and phosphorus in egg white and fibrin. . . . This is the foodstuff of the whole animal kingdom and is probably formed only by plants." In the *Bulletin* paper, the analogous phrase is *"pourrait se nommer Proteine de πρωτεῖος,* primarius," and, in its German translation in the *Journal für praktische Chemie,* this appears, *"könnte Protein von πρωτεῖος,* primarius, *genannt werden."* Later in the same paper, there occurs the sentence, *"Es wird aber nicht ohne Nutzen sein, die Untersuchungen des Körpers, den ich Protein genannt habe, noch weiter zu verfolgen."*

The internal evidence of the several papers, especially the use of the first personal pronouns, has seemed to most students of the matter (e.g., Vickery[9]) to point unmistakably to the conclusion that Mulder himself

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* These extremely rare journals were short-lived; only six volumes of the *Archief* (1833-1838) and three of the *Bulletin* (1838-1840) were published. There is a file of the *Archief* in the Library of the U. S. Patent office and one at the Massachusetts Institute of Technology and of the *Bulletin* in the Library of Congress.

A single number of the *Bulletin* contained 8 pages; Mulder's paper began on p. 104 of the issue (No. 13) dated July 15, 1838; this page carries the title and the first two paragraphs, and the date of issue accounts for the fact that the title does not contain the word protein as the title of the *Archief* paper does. The issue of July 30 (No. 14), pages 105 to 112 inclusive, contained more of the paper, and it is in these pages that the definition of protein is first given. The paper was completed in the issue (No. 15) dated August 15, 1838.

† This letter to Liebig was mentioned by Mulder in a letter to Berzelius dated August 17, 1838. He added that, "according to custom, it will be printed in the Annalen."

‡ The "plant albumin" to which he referred was a preparation of wheat glutenin obtained from gluten, after the gliadin had been removed by extraction with alcohol according to Beccari's technique, by solution in potassium carbonate and precipitation with acetic acid.

originated the term protein, and Sir Harold Hartley's discovery is therefore a matter of considerable surprise.

The source of his information was the collected letters of Berzelius published by H. G. Söderbaum in Uppsala in 1916.*[3] Volume 5 contains the correspondence between Mulder and Berzelius from 1834 to 1847. In the spring and early summer of 1838, Mulder had described his analytical studies of the proteins and had given his reasons for supposing that there is a radical common to all of these substances. On July 10, 1838, Berzelius wrote Mulder a long letter which contains the following sentences:

> "Or je présume que l'oxyde organique, qui est la base de la fibrine et de l'albumine (et auquel il faut donner un nom particulier p. ex. protéine) est composé d'un radical ternaire, combiné avec de l'oxygène dans quelqu'un de ses rapports simple que la nature inorganique nous présente."

and, later in the same letter,

> "Le nom protéine que je vous propose pour l'oxyde organique de la fibrine et de l'albumine, je voulais le dériver de πρωτειος, parce qu'il paraît être la substance primitive ou principale de la nutrition animale que les plantes préparent pour les herbivores et que ceux-ci fournissent ensuite aux carnassiers. En dérivant le nom du mot grec pour la fibre, il serait moins convenable, puisque l'oxyde organique est la base aussi de l'albumine et probablement de la matière colorante, ainsi que d'autres encore."

In his answer to this letter on August 17, 1838, Mulder makes frequent use of the word protein although he did not specifically acknowledge Berzelius' suggestion.

Why, then, if Mulder owed to Berzelius the suggestion of the word protein,† did he use the first personal pronoun in connection with it in several of his publications? The most likely explanation of this is that, in both the *Archief* and the *Bulletin* papers, Mulder in the first sentences acknowledged his general indebtedness to Berzelius for helpful comments and advice. Mulder was, at this time thirty-five years old (Berzelius was fifty-nine) and had only recently begun to make himself known for his

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*There is a complete set of Berzelius' letters[3] in the Historical Library of Yale University School of Medicine.

†Mulder had not asked Berzelius to suggest a name, but in a letter of March 29, 1838 he refers to *"les substances animales sans soufre et sans phosphore"* which combine with sulfur and phosphorus to form egg and serum albumin. Berzelius' suggestion was thus an attempt to provide a less awkward means of expression. He chose a Greek root which referred to its fundamental nature in nutrition in preference to one which referred to a property (i.e., fibrous nature) possessed only by certain individual substances. *"La matière colorante"* was hemoglobin.

chemical investigations. His correspondence with Berzelius, which had begun in 1834 over the matter of preparing a translation into Dutch of Berzelius' *Traité de Chimie,* had, by 1838, become voluminous. It was carried on in terms of the warmest admiration on his side and in a spirit of kindly helpfulness on that of Berzelius. In Söderbaum's phrase,[8] Mulder became a "corresponding disciple" of Berzelius, and the relationship continued, with every evidence of increasing mutual esteem and intimacy, until Berzelius' death in 1848.

Berzelius had for many years been the international authority for new chemical words; cystine and glycine are two examples in the amino acid field, and catalysis and isomerism are others which illustrate his genius even better. The word protein was not itself the significant point to Mulder, and Berzelius himself laid no unusual stress on it; he merely said it is necessary to have a name. That he felt no strong proprietary rights is plain from his report for 1838 in the *Jahresbericht*[10] where he writes, "Mulder names the organic substance, that is the chief component of fibrin and albumin, protein from πρωτειυω,* I take the first place." The word was a convenient one to express the fundamental idea Mulder was trying to convey and, at a time when new terms were frequently being introduced into chemistry, there did not seem to be any necessity to emphasize the precise origin of this one. Certainly, neither Mulder nor Berzelius could have had any clear idea of the importance it would assume after its connotation had been broadened and its meaning redefined as a result of the work of Liebig and the later generations of protein chemists. Wöhler, however, came to appreciate its value, for he wrote to Liebig[11] on February 19, 1848, at the height of the polemic with Mulder and in an effort to prevail upon Liebig to modify the asperity of his share in the discussion, that all of the personalities might well be overlooked in view of the fact that science had been enriched by the useful and appropriate word protein.

It is difficult to decide the exact date on which the new term was first published. Berzelius wrote his letter from Stockholm on July 10, 1838. Mulder at Rotterdam first employed the word in his paper in the issue of the *Bulletin* bearing the date July 30, 1838. Early in the paper is the statement that the author merely proposes to give a summary of his results and that the reader may consult the *Archief,* volume 6, for full details. This implies that the *Archief* paper, the title of which contains the word protein, was written before the paper in the *Bulletin.* The *Archief* paper is 75 pages

* In this instance, Berzelius employed the Greek verb as the root; previously he had suggested the adjectival form.

long and the *Bulletin* paper, in its German translation, 23 pages. It is almost incredible that Mulder could have written both of them between the receipt of Berzelius' letter of July 10th and the printing of the issue of the *Bulletin* dated July 30, and, in fact, there is no reason to assume that he did. It seems clear, from what Mulder wrote to Berzelius earlier in 1838, that his ideas on what came to be known as the "protein" hypothesis matured during the summer, and it is quite possible that he wrote much of the long *Archief* paper before he received Berzelius' letter. Save for the title, the word protein first occurs on page 128, rather more than halfway through. However, it is used at least once on no less than eighteen of the subsequent pages. This portion of the text must therefore have been written after the receipt of Berzelius' letter, and Mulder obviously wrote the title afterwards.

The *Bulletin* paper is, in effect, a condensation of a considerable part of the *Archief* paper. It is organized on the same plan; selected data are set forth in the first ten pages in support of the hypothesis that there is a radical common to several, at least, of the better known albuminous substances; the term protein is then defined in the language quoted above and is used on the next two pages several times. It does not occur again until the author mentions "proteinsulfuric acid" on the last two pages. In the *Journal für praktische Chemie* translation,[8] the translator added a note that the subject is "to be continued," and there are subsequent short papers in volume 16, one dealing with leucine and glycine[12] and another with "xanthoproteic acid,"[13] a term newly coined by Mulder for the "yellow acid" of Fourcroy and Vauquelin. Both of these subjects are discussed in the long *Archief* paper and also in separate short articles in the *Bulletin*.[14]

Little can be concluded from this except that the first few pages of the *Bulletin* paper *could* have been written before the receipt of Berzelius' letter. However, the general impression given is that most of the text was drafted after this letter reached Mulder. Accordingly, it would seem that the *Archief* paper was, for the most part, prepared before the *Bulletin* paper and it appears to be the first in which the term "protein" was used. Whether volume 6 of the *Archief* came from the printer in advance of the semi-monthly number of the *Bulletin* which bears the date July 30, 1838, remains in question.

There is some evidence on the time of appearance of the papers in the correspondence between Berzelius and Mulder. On March 29, 1838, Mulder wrote that "five numbers of the *Bulletin* and one number of the *Archief*, number 4, the last of 1837" had recently been sent. The *Archief* was apparently issued in four parts per year. On November 24, 1838, he

mentioned that he had sent "several numbers of the *Bulletin* and numbers one and two of the *Archief*" a short time previously. The paper "Over Protein" must have been included in these numbers of the *Archief*, for Mulder asked Berzelius, in a letter of January 8, 1839, to refer to pages 130 and 141 of the last number of the *Archief*, "which you have doubtless received."

The *Archief* paper was thus certainly in print in November 1838, and, since the *Bulletin* paper begins on page 104 and at least five numbers of this journal had been sent to Berzelius early in the year, there seems little doubt that this paper was also included in the package sent to Berzelius in November. However, this sheds little light upon which of the two papers became available to the public first.

One further point in connection with the discovery of the Berzelius letter should be emphasized because of its later importance in protein chemistry. This is the statement by Berzelius that protein (i.e., the radical) is the fundamental substance in nutrition and is synthesized by plants *"pour les herbivores et que ceux-ci fournissent ensuite aux carnassiers."* Mulder repeated this idea, as is shown in the quotation from the *Archief* paper above, and enlarged on it to some extent both in this and in the *Bulletin* paper.

Liebig, a few years later, after he had, with his students, investigated the ultimate composition of several animal and plant proteins, became convinced of the essential identity of plant and animal proteins of corresponding solubility, and on June 28, 1841[14] he wrote to Wöhler: "We now have a complete analogy; we have plant albumin, plant fibrin, and plant casein all identical with each other and with the animal proteins that bear the same name. One can assert that the animal organism contributes merely the form of its blood." Without acknowledgment to Mulder, and still less to Berzelius, of whose statement he was doubtless unaware, Liebig pursued the implications of this idea. The doctrine that there are only four fundamental proteins in nature, namely, albumin, fibrin, casein, and gelatin, was enunciated[15] and, although the work of Ritthausen in the later decades of the century demonstrated it to be a gross over-simplification, this doctrine dominated the early years of protein chemistry and was finally refuted only in the first decade of the present century, largely through the work in this country of Osborne and his collaborators, especially Wells, who first demonstrated the complete specificity of the proteins of plant seeds. To the early workers, however, who had no means of estimating their molecular weight, proteins were relatively simple organic compounds which passed

from the plant into the animal metabolism with only minor change. The true complexity of the protein molecule has been fully appreciated only during the past few decades.

Berzelius' two contributions, the name and the notion of the fundamental role of the plant in protein metabolism, have undergone great modifications in the past century. Protein chemists may still, however, marvel at the genius which grasped the essential fact that the proteins occupy the first place in animal nutrition and thus in the truly essential affairs of mankind.

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STUDIES OF ELECTROPHORETIC SERUM PROTEIN PATTERNS IN SUBJECTS TREATED WITH PITUITARY-ADRENAL CORTICAL HORMONES, NITROGEN MUSTARD, OR X-RADIATION*

JULIAN FRIEDEN† AND ABRAHAM WHITE‡

Investigations during the past ten years have formed the basis for the working hypothesis that pituitary-adrenal cortical secretion exerts an influence on the structure and function of lymphoid tissue. The administration to rats of adrenal cortical extract, or of adrenal cortical steroids oxygenated in position 11 of the steroid nucleus, produced marked thymic atrophy.[26, 27, 35, 40, 44, 48] Experiments conducted by Dougherty and White[10] demonstrated that adrenal cortical secretion, regulated by the pituitary adrenotrophic hormone, is a normally existing mechanism which can affect lymphoid tissue mass. At a time when lymphoid tissue involution was maximal as a result of augmented pituitary-adrenal cortical secretion, a profound absolute lymphocytopenia was observed.[11] Histological studies revealed [10, 12] that the basis for these phenomena was the marked dissolution of lymphocytes in the lymphoid organs following augmented pituitary-adrenal cortical secretion. Thus, decreased lymphoid tissue weight was due to fewer lymphocytes in the lymphoid organs, and the lymphocytopenia appeared to be due to a failure of delivery of lymphocytes to the circulation because of their dissolution within the lymphoid organs.

It was further established by White and Dougherty,[50] and confirmed by Kass,[29] that lymphocytes contain a protein which is identical with serum globulin. Moreover, in the immunized animal, antibody globulin was demonstrated in the lymphocytes of mice[8] and of rabbits.[19] It is well known that the antibody of the blood is generally found in the β- and γ-globulin fractions.[16] This led to experiments which demonstrated that a single injection of adrenal cortical extract (aqueous or oil), or of adrenotrophic

* From the Department of Physiological Chemistry. The data presented herein are taken, in part, from a thesis submitted by Julian Frieden to the faculty of the Yale School of Medicine in partial fulfillment of the requirements for the degree of Doctor of Medicine. This work was aided by a grant from The American Cancer Society on recommendation of The Committee on Growth of The National Research Council.

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hormone, in hyperimmunized rabbits resulted within six hours in a marked rise in antibodies in the blood.[5, 9, 14] The data established that higher titers of antibody appear in the immunized animal after adrenal cortical administration at a time when lymphocyte dissolution in the tissues is most marked, and when the most striking lymphocytopenia is present in the blood.[51]

The influence of pituitary adrenotrophic hormone on lymphoid tissue structure and function appears to offer an explanation for the similarities of changes in lymphoid tissue following many unrelated stimuli. Sayers *et al.*[42] have reviewed the literature suggesting that most of these stimuli augment the secretion of pituitary adrenotrophic hormone. This hypothesis would also explain why various nonspecific agents produce an anamnestic response[4] and would correlate this response with the concomitant lymphocytopenia.

With this background of experimental evidence, it was proposed to study the serum protein pattern in dogs and in human subjects receiving either adrenal cortical extract or pituitary adrenotrophic hormone. In addition, it has been possible to examine in the Tiselius apparatus the electrophoretic serum protein patterns of patients receiving x-ray irradiation or nitrogen mustard therapy. The radio-sensitivity of lymphoid tissue has long been known.[7] Several investigators have studied the possible effects of x-ray therapy on serum proteins.[8, 9, 13, 25] Inasmuch as the majority of the previous studies in this field have utilized chemical rather than electrophoretic measurements, it was considered desirable to examine the effect of x-radiation on the electrophoretic pattern of the serum proteins.

Nitrogen mustard therapy, in use currently in treatment of various lymphomata, is known to produce within 24 hours a marked lymphocytopenia, which becomes progressively more severe during the subsequent six to eight days.[28] Similar observations have been made in experimental animals[19] treated with nitrogen mustard. It was thought protein changes might be found at a time when lymphocyte destruction was striking.

Procedure and methods

All blood samples were drawn under oil, with a minimum of stasis. The blood was allowed to clot and the clear serum separated.

Total nitrogen analyses were conducted in duplicate by the macro-Kjeldahl technique, using mercuric oxide as a catalyst.

The method of Bock and Benedict[2] was employed for non-protein nitrogen determinations.

For electrophoresis, the Tiselius apparatus[33, 47] with the Philpot scanning device[39]

was employed. Four ml. of serum were diluted to 12 ml. with 0.1 molar veronal buffer (pH 8.6). The diluted serum was then dialyzed for 48 to 72 hours at 5° C. against two liters of the buffer.

Electrophoresis was conducted at approximately 2° C., using a potential gradient of 5 to 6 volts per cm. Each electrophoretic run was continued until complete separation of components occurred. Photographs were taken and the magnified projections of the plate diagram then traced. The areas under the peaks were measured with the planimeter, thus giving the relative percentages of the individual serum components. The descending boundary was used for measurements of all fractions except the β-globulin. Because of the lipid anomaly in this fraction of the pattern in the descending

TABLE 1

ELECTROPHORETIC SERUM PROTEIN PATTERNS IN DOGS INJECTED WITH ADRENAL CORTICAL EXTRACTS*

Dog #1	*Pre-injection*		*3 hrs. post-injection*	
	gm./%	*%*	*gm./%*	*%*
S.T.P.†	6.17		6.46	
Albumin	2.59	42.0	2.90	44.7
α_1-Globulin	0.76	12.3	0.85	13.1
α_2-Globulin	0.77	12.5	0.93	14.4
β-Globulin	1.30	21.2	1.10	17.5
γ-Globulin	0.74	11.9	0.66	10.3
Dog #2	*Pre-injection*		*3 hrs. post-injection*	
	gm./%	*%*	*gm./%*	*%*
S.T.P.†	6.53		6.58	
Albumin	3.90	61.1	3.74	57.0
α_1-Globulin	0.54	8.3	0.74	11.2
α_2-Globulin	1.03	15.7	0.79	12.0
β-Globulin	0.48	7.4	0.65	9.8
γ-Globulin	0.48	7.4	0.65	9.8

*Each animal received 12 ml. of aqueous adrenal cortical extract (Upjohn) subcutaneously.

†S.T.P.—Serum total proteins.

limb, the ascending limb pattern was utilized for β-globulin measurements in most of the experiments. In instances where the total protein concentration of the serum had been determined, the absolute number of grams of each fraction could be calculated from the percentage distribution of the various fractions.

Results

Tables 1 and 2 contain data obtained from electrophoretic examinations of the sera of dogs and human subjects injected with either adrenal cortical extract or pituitary adrenotrophic hormone. It will be seen from the tables

that no consistently striking alterations in the serum protein pattern occurred in any of the subjects studied.* This was surprising in that a concomitant lymphocytopenia was present in many instances. The observed

TABLE 2

ELECTROPHORETIC SERUM PROTEIN PATTERNS FOLLOWING PITUITARY ADRENOTROPHIC HORMONE OR ADRENAL CORTICAL EXTRACT INJECTIONS IN MAN*

Patient Diagnosis†		*Serum Protein (%)* *Albumin*	*Globulins* α_1	α_2	β	γ	*Total blood lymphocytes*
Patient #1	Before	63.2	2.4	12.0	11.0	11.3	3010
	After 4 hrs.	61.7	2.8	9.8	13.7	11.9	3390
Patient #2	Before	65.7	3.3	9.8	9.8	11.3	1750
	After 4 hrs.	62.9	4.0	10.2	9.5	13.3	2110
Patient #3	Before	68.8	2.8	6.7	11.0	10.6	4140
	After 4 hrs.	67.8	3.6	7.7	7.7	13.1	2500
Patient #4	Before	61.0	5.8	10.1	10.5	12.6	2070
	After 4 hrs.	59.3	6.2	11.9	10.4	12.1	1780
	After 8 hrs.	65.5	5.6	10.3	9.1	9.4	2540
Patient #5	Before	56.3	3.5	8.2	9.8	22.2	2160
	After 4 hrs.	56.5	3.7	8.1	9.6	22.0	1430
Patient #6	Before	44.8	6.7	17.6	9.1	21.7	37,765
	After 4 hrs.	43.0	7.3	16.3	10.5	22.7	18,644

* Patients #1 to #5 were injected with 25 mgm. adrenotrophic hormone intramuscularly. Patient #6 received 15 cc. adrenal cortical extract (Wilson) intramuscularly.

† Patients #1 to #4 were cases of dementia praecox.
#5 was a normal man.
#6 was a patient with infectious mononucleosis.

* The data for dog #2 in Table 1 suggest that distinct increases in circulating α_1-, β-, and γ-globulins may have occurred following hormone administration. A similar trend is seen in the γ-globulin fractions of patients #2 and #3 following injection of hormone (Table 2). However, such trends are seen in too few instances to be considered significant.

lymphocytopenia is in good agreement with that originally demonstrated by Dougherty and White[31] to occur within a few hours following subcutaneous injection of either adrenal cortical extract or pituitary adrenotrophic hormone in mice, rats, rabbits, dogs, and humans. These authors postulated that pituitary-adrenal cortical secretion is one of the normal mechanisms influencing the level of circulating lymphocytes. The lymphopenic effect of pituitary-adrenal cortical secretion has been confirmed in a number of laboratories.[49]

The negative findings with respect to the serum protein changes in the human following adrenal cortical hormone administration are in agreement with certain other available data.[49] Milne and White[34] were unable to obtain consistent alterations in the serum protein patterns of mice injected with adrenal cortical extract. Li and Reinhardt[32] presented data showing an increase in albumin to globulin ratios in the sera of hypophysectomized rats treated with growth or adrenotrophic hormones. There was no increase in the globulin fractions of either hypophysectomized or normal rats injected with adrenotrophic hormone. These authors also found no change in the protein pattern of cervical duct lymph after adrenotrophic hormone administration.

The further experiments in the present study were designed to examine possible alterations in serum proteins under circumstances, other than extraneous hormone administration, which are associated with marked lymphoid tissue involution or lymphocyte dissolution. One of the most effective methods for the production of lymphoid tissue involution is x-ray irradiation. The decrease in lymphoid tissue size seen following exposure to x-rays is one of the most clearly established clinical and experimental observations. Of considerable interest in this connection is the equally well-documented observation that the dose of radiation required to cause lymphocyte dissolution *in vitro* is many fold that required *in vivo*. (See reviews of Dunlap,[15] Selling and Osgood,[43] and Murphy.[38]) This has led numerous investigators to suggest that a humoral mechanism may be concerned with the lymphocytolytic action of x-rays. This working hypothesis would aid in explaining the clinical observation that following irradiation of a lymphoid structure in the body, involution of distant nodes occurs frequently. Experimentally, Barnes and Furth[1] showed that, in a pair of parabiotic mice, the shielded animal has extensive lymphoid tissue destruction if his mate is irradiated, suggesting the involvement of a humoral mechanism. Of particular significance are the experiments of Leblond and Segal,[21] who shielded all but the thymic area of normal and adrenalectomized

rats and exposed this region to 3000 Roentgen. In the unoperated rats, there was generalized lymphoid, as well as thymic involution, whereas only thymic degeneration occurred in the adrenalectomized animals.

Dougherty and White[13] used x-radiation as a means of producing lymphocyte dissolution in mice in the absence of the adrenal glands. These authors found that in addition to the well-known acute lymphocytopenic action of x-rays, the total proteins and the γ-globulin fraction of the blood increased at a time when tissue lymphocytolysis and blood lymphocytopenia were most marked. Davy[6] had found that there was an immediate drop in globulin following irradiation of dogs, but that in 24 hours it was either at the pretreatment level or higher. This work agreed with that of Herzfield and Schinz,[25] although Breitlander and Lasch[5] had found no change in serum proteins under similar conditions.

From the foregoing evidence, one might anticipate alterations in the serum globulin levels of patients as a result of extensive lymphoid tissue dissolution due to radiation. It will be seen, however, from the data presented in Table 3, that no consistent alterations in serum protein patterns were found in the four patients examined at various intervals during and following x-radiation therapy. In only one case (patient A, Table 3) was a rise in the globulin fraction of the blood proteins seen following a course of x-ray therapy.

Another agent which is known to have a destructive effect on lymphoid elements is the nitrogen mustard, methyl-bis (beta-chloroethyl) amine hydrochloride. This agent causes a marked lymphocytopenia, progressive for 6 to 8 days, with an accompanying striking disappearance of lymphocytes from lymphoid organs.[18, 28, 30] It has been possible in the present study to examine the serum proteins of five patients before, and at varying intervals following, administration of nitrogen mustard. The data are presented in Table 4. In 3 of the 5 patients studied, the results suggest a trend toward a decrease in either the β- or the γ-globulin fractions, or both, following therapy with nitrogen mustard. However, there is no correlation between the decrease in peripheral lymphocytes and the degree of the protein changes, since marked lymphocytopenias were seen in patients both with and without serum globulin alterations. It may be pointed out here that a quantitative relationship need not exist between the level of circulating lymphocytes and the concentration of a blood constituent derived from these cells. This is due to the fact that lymphocytopenia may be a result of either failure to produce new lymphocytes, in which case there will also be a reduced production of lymphocytic components, or a failure to deliver

TABLE 3

ELECTROPHORETIC SERUM PROTEIN PATTERNS FOLLOWING X-RAY IRRADIATION IN MAN

		Time after treatment				
	Before treatment	6 *hours*	7½ *hours*	9 *days*	14 *days*	1 *month*
Patient A[a]						
S.T.P.* Gm./%	6.54	6.52		7.08		
Albumin %	68.2	64.2		60.1		
α_1-Globulin %	5.5	5.7		5.4		
α_2-Globulin %	10.9	11.1		11.8		
β-Globulin %	9.2	12.0		15.5		
γ-Globulin %	6.2	6.9		7.2		
Patient B[b]						
S.T.P.* Gm./%	6.7	7.38				
Albumin %	54.6	56.8				
α_1-Globulin %	6.75	4.76				
α_2-Globulin %	13.8	13.7				
β-Globulin %	18.08	19.05				
γ-Globulin %	6.75	7.14				
Patient C[c]						
S.T.P.* Gm./%	6.76		6.75			7.46
Albumin %	56.1		59.8			53.5
α_1-Globulin %	2.75		2.9			4.5
α_2-Globulin %	9.35		8.7			9.8
β-Globulin %	10.5		10.7			11.4
γ-Globulin %	21.4		17.9			20.4
Patient D[d]						
S.T.P.* Gm./%	6.2					
Albumin %	62.9				60.9	
α_1-Globulin %	5.9				6.1	
α_2-Globulin %	11.7				13.9	
β-Globulin %	13.2				11.8	
γ-Globulin %	6.2				7.2	

[a] Man with carcinoma of larynx, received approximately 38 R/min. for 6-7 minutes (7 cm. field) every day for 8 days.

[b] Woman received deep irradiation to pituitary fossa. (Followed by vomiting and probable dehydration.)

[c] Man with chronic lymphatic leukemia. 7 treatments of spray irradiation over thorax and abdomen (11 R/min. for 2-3 minutes.) Over this period white blood-cell count dropped from 144,000 to 14,000.

[d] Woman with carcinoma of breast with pulmonary metastases. Deep therapy to dorsal spine.

* Serum total proteins.

TABLE 4
ELECTROPHORETIC SERUM PROTEIN PATTERNS FOLLOWING NITROGEN MUSTARD THERAPY*

		Days following final injection					
	Before treatment	1 day	3 days	4 days	6 days	10 days	12 days
Patient A[a]							
S.T.P.† Gm./%	6.85	6.26				5.80	
Albumin %	45.2	50.6				43.9	
α_1-Globulin %	9.5	9.7				13.0	
α_2-Globulin %	16.6	17.5				16.2	
β-Globulin %	11.7	12.8				13.5	
γ-Globulin %	16.8	9.2				13.3	
T.B.L.‡	425					175	
Patient B[b]							
S.T.P.† Gm./%	7.05				7.50		
Albumin %	68.8				67.0		
α_1-Globulin %	4.1				5.3		
α_2-Globulin %	8.8				9.7		
β-Globulin %	8.8				8.9		
γ-Globulin %	9.5				9.1		
T.B.L.‡	3390				425		
Patient C[c]							
S.T.P.† Gm./%	6.93		7.10				
Albumin %	50.2		55.3			66.1	
α_1-Globulin %	7.6		5.2			5.6	
α_2-Globulin %	15.2		11.7			8.6	
β-Globulin %	11.8		11.9			7.2	
γ-Globulin %	15.2		15.8			12.5	
T.B.L.‡	3248		882			1125	
Patient D[d]							
S.T.P.† Gm./%	5.70			4.86			
Albumin %	46.2			45.3			
α_1-Globulin %	11.7			16.2			
α_2-Globulin %	15.9			16.2			
β-Globulin %	17.7			13.1			
γ-Globulin %	8.6			9.3			
T.B.L.‡	861			335			
Patient E[e]							
S.T.P.† Gm./%							
Albumin %	39.0						43.1
α_1-Globulin %	7.8						6.8

			Days following final injection					
		Before treatment	1 *day*	3 *days*	4 *days*	6 *days*	10 *days*	12 *days*
α_2-Globulin	%	14.5						12.6
β-Globulin	%	16.0						14.6
γ-Globulin	%	22.7						22.8
T.B.L.‡		4550						700

[a] 33-year-old female. Known Hodgkins disease for 8 months. Several x-ray treatments previously. After nitrogen mustard, nodes and breast mass decreased in size. Less dyspnea and pain.

[b] 37-year-old man. Pulmonary metastases of myxosarcoma of thigh. Under therapy there was marked pain relief.

[c] 30-year-old man. Hodgkins disease, 1 year. Had received x-ray therapy previously. Back pain improved following treatment.

[d] 47-year-old man. Bronchogenic carcinoma. 25-pound weight loss.

[e] Young adult man with Hodgkins disease. No previous therapy.

* All patients received 0.1 mgm. of nitrogen mustard per kilogram every day for 4 days.

† Serum total proteins.

‡ Total blood lymphocytes.

normal numbers of lymphocytes to the circulation, despite normal lymphocyte production. The former case is seen in chronic nitrogen mustard or x-ray therapy where damage to lymphocyte production is a primary factor. On the other hand, adrenal cortical steroids produce lymphocyte dissolution in the nodes, and, if this continues, fewer cells are delivered to the blood. In this instance, the components of destroyed lymphocytes are still available for addition to the circulation, even though the number of lymphocytes is reduced.

A single dose of x-rays has been reported to produce globulin rises in well-nourished animals.[13] However, repetition of these experiments, while revealing increases in total serum proteins, showed no changes in the relative amounts of the individual protein components of the serum.[34] Moreover, chronic radiation is known to depress antibody globulin production,[20, 22, 23, 37, 45] as do such leukotoxic agents as benzene,[21, 40] sulfur mustard,[24] and nitrogen mustard.[38] Apparently under these circumstances there is a destruction of the chief tissue contributing to the synthesis of new globulin, and this results in an ultimate depression of the serum globulin levels. Philips, Hopkins, and Freeman[38] demonstrated a delayed increase in the circulating antibodies in goats treated with nitrogen mustard following antigen injections, as compared with animals receiving antigen alone. These authors pointed out that nitrogen mustard may act directly on the lymphoid elements without endocrine mediation,[50] thus causing persistent lymphoid

involution which may not necessarily be associated with the release of stored antibody. It is of some interest that the animals which had been given nitrogen mustard were capable of showing an anamnestic reaction, despite lymphocyte depletion of lymph nodes. This observation suggested that under conditions of lymphoid depletion, antigenic stimulation may be effected in other immunologically active tissues containing reticuloendothelial elements. With this viewpoint, it is perhaps possible to understand why no striking diminution in β- and γ-globulins occurred in patients given chronic doses of nitrogen mustard, since other cell types may participate in globulin production.

The present study has sought to investigate further the possible contribution of the lymphocyte to the production of serum β- and γ-globulins. The data presented, however, suggest that there were no consistent changes in serum globulins in conditions which might be classified broadly as characterized by either pituitary-adrenal cortical induced lymphocyte dissolution (hormones, x-ray, or nitrogen mustard), or by an apparent lack of lymphocyte formation (nitrogen mustard). These essentially negative results suggest that a number of as yet unevaluated factors may be of significance in establishing lymphocytes as a significant source of serum globulins. The techniques of measurement employed may not be adequately sensitive to detect changes which perhaps did occur. In a human subject with a blood volume of 5 liters, the addition of at least 15 grams of protein to the circulation is necessary to produce a 5 per cent rise in total blood proteins. Moreover, this addition must be continuous to compensate for the removal of protein in the peripheral circulation. It may also be noted that a significant degree of hemodilution may occur as a result of increased secretion of adrenal cortical steroids, thus obscuring significantly elevated concentrations of blood components.

Evaluation of the blood level of cellular elements, or of the protein elements derived therefrom, requires consideration of a diversity of variables. The first of these is the structural and physiological integrity of the tissues concerned with the synthesis of the cells and their constituents. For example, destruction of the synthetic site by x-ray or nitrogen mustard would impair both synthesis and delivery to the circulation of the lymphocytes. Secondly, the supply and quality of materials from dietary sources for the construction of new cells is of prime importance. Thus, Wissler and his colleagues[82] have demonstrated that, under conditions of undernutrition, globulin synthesis is greatly impaired. In addition, there are several processes occurring at the site of synthesis whose rates may be affected by

endocrine secretions. These processes are (a) the rate of new cell (and its constituents) synthesis, (b) the rate of continuing cell turnover at the site of synthesis, (c) the rate of delivery of cells and/or their constituents to the circulation. Finally, the blood levels of a particular cell, or of constituents derived therefrom, may be affected by the rate at which the reticulo-endothelial system removes these materials from the circulation. The rate of this process may also be influenced by endocrine secretions. Indeed, Reiss and Gothe[41] reported that the capacity of reticulo-endothelial cells to store a circulating dye is increased one hour after injection of an extract rich in adrenotrophic hormone. Furthermore, Gordon and Katsh[17] showed a relation between the activity of the adrenal cortex and the capacity of reticulo-endothelial cells to take up injected thorium oxide. Other factors, such as renal loss and passage into tissues, may also be of significance in the removal of blood constituents from the circulation.

Thus, the maintenance of the normal state of lymphoid tissue function, and of its contributions to the circulation, is a result of a dynamic balance among a number of processes. One or more of these may be affected by experimental or clinical conditions, and until a clear evaluation of the contribution of each is available, unequivocal interpretation of data derived from studies of the type presented here is not possible.

Summary and conclusions

1. No significant alterations in serum protein levels were seen in man or in dogs following a single injection of adrenotrophic hormone or adrenal cortical extract.

2. X-ray irradiation of several patients with carcinomata produced no consistent changes in serum protein levels.

3. Nitrogen mustard administration had no definite effect on the serum proteins, despite a marked involution of the lymphoid tissue throughout the body.

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INDUCTION OF THE LUPUS ERYTHEMATOSUS ("L.E.") CELL IN VITRO IN PERIPHERAL BLOOD*

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In 1948, Hargraves, Richmond, and Morton[2] described a new type of cell observed in bone marrow preparations of patients with acute disseminated lupus erythematosus. This cell appears to be a mature polymorphonuclear leukocyte which has within its cytoplasm a large homogeneous mass of blue staining material which displaces the nucleus to the periphery of the cell. Since the cell has been observed only in patients with acute lupus erythematosus, these investigators have called it the "L.E." cell. In these same preparations they described other cellular forms which they thought might be precursors in the formation of the L.E. cell. In a subsequent article[1] the same investigators described the production *in vitro* of the L.E. cell phenomenon by incubating normal bone marrow with the plasma from patients with acute disseminated lupus erythematosus. Haserick and Bortz[3] confirmed the *in vitro* production of the L.E. cell and suggested that this be used as a diagnostic test. Following the report by Sundberg and Lick[4] that they had observed the L.E. cell in the peripheral blood of patients with acute lupus erythematosus, Hargraves[1] also noted the presence of these cells in peripheral blood preparations in very small numbers. However, it was necessary to centrifuge the heparinized or citrated venous blood in a specially designed flask in order to have an adequate "buffy coat" from which to make the smear.

The present investigation was carried out in an attempt to produce the L.E. cell in the peripheral blood by incubating the cellular elements of normal whole blood with plasma from patients with acute disseminated lupus erythematosus. The leukopenia usually seen in acute lupus erythematosus presents a problem because of the small number of leukocytes available for examination during the search for the L.E. cell. By the method of using the "buffy coat" from the peripheral blood of the normal subject which had been incubated with plasma from a case of acute disseminated lupus erythematosus the probability of finding the L.E. cell seemed more favorable.

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Method

Plasma from a case of acute disseminated lupus erythematosus was incubated with cells from normal subjects and the "buffy coat" was examined for L.E. cells. Control studies consisted of the incubation of normal cells with normal plasma in place of the plasma from the patient with lupus. A detailed description of the method follows.

Five cc. of venous blood from a patient with acute disseminated lupus erythematosus were collected in bottles containing balanced oxalate crystals (4 mg. potassium oxalate plus 6 mg. ammonium oxalate). The whole blood was centrifuged for ten minutes at 2000 RPM, and the plasma was pipetted off and saved.

Five cc. of venous blood from each of five normal subjects were collected in a similar way and each five-cc. specimen was treated in the following manner. One cc. of blood was placed in a Wintrobe hematocrit tube. Two cc. of the blood were placed in each of two five-cc. test tubes, and these two tubes were centrifuged for five minutes at 2000 RPM. The plasma was carefully pipetted off from each test tube and saved. To one test tube was added one cc. of the plasma previously prepared from the blood of the patient with acute lupus erythematosus. To the other test tube, which was used as a control, was added one cc. of plasma from another normal subject. These two test tubes were agitated gently to mix thoroughly the cellular elements and plasma and then incubated at a temperature ranging from 34° C. to 37° C. for twenty-five minutes. The tubes were agitated once during incubation and again at the end of twenty-five minutes. After incubation two Wintrobe hematocrit tubes were filled with the cells and plasma preparations. These two hematocrit tubes, along with the normal subject's control hematocrit tube, were centrifuged for ten minutes at 2000 RPM. The plasma was carefully pipetted off from each and discarded, and a single drop of the "buffy coat" was placed on a clean glass slide. A thin smear was made in the usual manner and stained with Wright's stain. Each slide was searched for thirty minutes, using an oil immersion lens.

For each of the five normal subjects in this series three slides were prepared: slide No. 1 contained the untreated "buffy coat"; slide No. 2 contained the "buffy coat" which had been incubated with the plasma from the patient with acute disseminated lupus erythematosus; and slide No. 3 contained the "buffy coat" which had been exposed to the plasma from another normal subject.

In addition to the plasma from the case of lupus erythematosus, plasma from three other patients was incubated with the normal cellular mixture and smears made as described above. Clinically these three patients had acute rheumatic fever, rheumatoid arthritis, and an acute sensitivity reaction to penicillin, respectively.

Results

In the untreated "buffy coat" smear from a patient with acute lupus erythematosus, L.E. cells were consistently observed in small numbers. In every slide prepared with normal "buffy coat" treated with plasma from

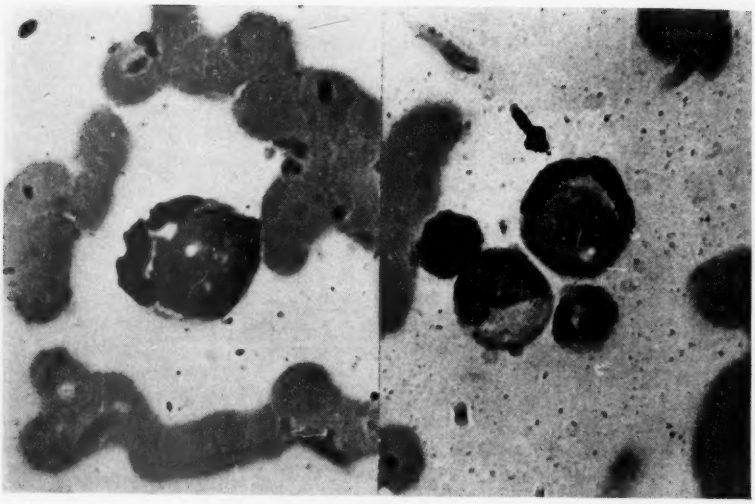

FIG. 1. Photomicrographs of L.E. cells from slides prepared with normal "buffy coat" treated with plasma from patient with acute disseminated lupus erythematosus.

this same patient with acute disseminated lupus erythematosus one or more L.E. cells were seen (Fig. 1). No L.E. cells were demonstrable in any of the control slides.

Discussion

The presence of the L.E. cell in the peripheral blood of patients with disseminated lupus erythematosus has been confirmed in these studies. In addition, these observations demonstrate that the polymorphonuclear leukocyte in the peripheral blood of a normal individual will assume the characteristic appearance of the L.E. cell after incubation with plasma from a patient with disseminated lupus erythematosus. The mechanism of the production of the L.E. cell is obscure. It may be that the polymorphonuclear leukocyte has been acted upon by the lupus plasma to cause it to phagocytize cellular debris. Or possibly the plasma from the patient with lupus erythematosus causes nucleolysis of certain of the normal cellular elements, which, in turn, are then phagocytized by polymorphonuclear leukocytes.

Hargraves[1] noted the difficulty of isolating the L.E. cell in the peripheral blood of patients with acute disseminated lupus erythematosus because of the paucity of leukocytes concomitant with this illness. The use of normal peripheral blood containing adequate numbers of leukocytes treated with plasma from a patient with lupus erythematosus would alleviate this aspect of the problem. This procedure technically simplifies to a great extent the induction of the L.E. cell for diagnostic purposes in suspected cases of acute disseminated lupus erythematosus.

Summary

1. The L.E. cell has been found in the peripheral blood of patients with acute disseminated lupus erythematosus.

2. The L.E. cell can be induced by cross incubation of cellular elements from normal peripheral blood with the plasma from a patient with lupus erythematosus.

3. The induction of the L.E. cell using the method described in this study simplifies the diagnostic test for acute disseminated lupus erythematosus.

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TRANSDUCERS FOR MULTICHANNEL STUDIES IN NEUROPHARMACOLOGY*

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In determining cause and effect of physiological events during experimental procedures, time relationships are of primary importance. At the present time, the effect of drugs on such functions as respiration, blood pressure, and organ motility are measured by using the smoked drum kymograph, while the electrocardiogram, electrocephalogram, and nerve or muscle action potentials are measured with separate instruments. Frequently additional animals must be used to complete these several recordings. When the mechanical and electrical recordings are combined in the same system, duplication of an experiment to obtain the additional data is unnecessary. Moreover, since the recordings may be simultaneous, any interrelation of one functional event with another can be determined.

Multichannel electroencephalographs are now available in most laboratories. These instruments incorporate high gain resistance-capacitance coupled amplifiers operating ink-writing oscillographs. With these instruments it is necessary only to convert the mechanical forces or displacements activating the usual mechanical levers or manometers into electrical current variations. Also, the amplifiers are sufficiently flexible to record the action currents from brain, nerve, and muscle. It thus becomes practical to combine the classical kymographic recordings with electrophysiological measurements. The multiple recording technique to be presented here describes the necessary alterations of the multichannel amplifiers and the construction of apparatus (i.e., transducers) required for translation of mechanical into electrical forces.

Electrical means are particularly suitable for the measurement of the variety of mechanical strain, pressure, and volume changes encountered in pharmacological research since they permit a combination of high fidelity of response, a wide variety of sensitivities and instantaneous visualization, and a permanent record of the phenomena under observation. The devices used to convert mechanical into electrical energy

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are classified as transducers. A variety of methods for transforming energy states have been utilized. The bonded resistance wire strain gage is incorporated into transducers for measuring (a) alterations produced on the surface of the skin by arterial pulse,[2, 3] (b) intra-arterial blood pressure,[5] and (c) movements occurring in the pregnant uterus.[9] Transducers employing magnetic reluctance[4] and electrical capacitance[6] changes produced by metal membrane manometers have also been used for recording blood pressure activity. A differential manometer utilizing a Venturi pitot tube activating a metal membrane whose changing position alters magnetic reluctance was used for recording blood flow through large arteries.[8] Thermistors have been adapted to the measurement of temperature inside blood vessels, subsurface tissues, or external orifices.[1] Changes in the electrical capacity (impedance) of cavities have been applied to the detection of changes of heart and chest volume.[11] These procedures have, however, all incorporated an additional recording device, usually the photo cell recording galvanometer.

The output signal from the various transducers is quite small and has power enough only to operate delicate galvanometers. For practical purposes the signals are amplified by the electroencephalograph amplifiers until an ink-writing pen can be operated.

The development of the use of these transducers and their inclusion into the simultaneous multiple recording scheme has already been found of value in the study of certain neuropharmacological problems. Because of their greater utility and more widespread application, we have limited ourselves to the description of transducers for measuring and recording fluid pressures and respiratory activity. However, the diversity of problems that can be solved with the aid of this technique should be limited only by the ingenuity and need of the investigator.

Adaptation of the electroencephalograph amplifiers for use with transducers. In many biological phenomena an equilibrium status is maintained for considerable periods of time. Mean blood pressure, smooth muscle tone, body temperatures, and DC potentials are examples. While these physiological events do undergo slow changes, for all essential purposes the output signal from the transducers is a constant electrical quantity (potential difference or current flow). A continuously applied constant signal will not, however, pass through the resistance-capacitance coupled amplifiers (a DC coupled amplifier might be used). The time constants of the RC coupled amplifiers limit the type of signal which can be amplified to one which is rapidly changing in character. Thus for this type of physiological event, e.g. blood pressure, it becomes necessary to adopt the use of the carrier-current amplifier system.

In the carrier-current amplifier system an oscillatory "carrier wave" is provided for passage through the amplifiers. The signal from the transducer modifies or modulates the carrier wave so that the amplitude of each wave peak is proportional to the magnitude of the applied transducer signal. In

this system the transducer output after amplification is represented by a proportional excursion of the pens both above and below the zero line, i.e., the greater the blood pressure, the wider will be the band of pen tracings. The pens will attempt to follow the carrier wave oscillations as much as the limitation of their inertia will permit. The resultant noise and spatter of ink is objectionable. This objection is abolished if the modulated carrier wave is rectified or demodulated, removing the oscillatory waves from the amplified transducer signal.

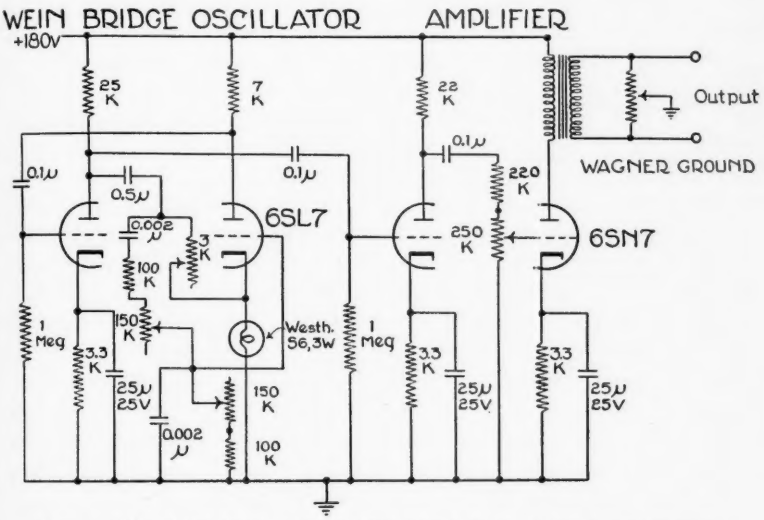

FIG. 1. Wein bridge phase shift oscillator supplying an 800-cycle carrier wave.

In practice, the modulated carrier wave is amplified by the RC coupled amplifier through four push-pull stages (see Fig. 2). The signal from the plates of the last 6SK7 pair is then interrupted beyond the coupling capacitor, fed through the demodulator, and returned to the grids of the 6L6 power amplifiers.

Carrier wave oscillator. Simple vacuum tube oscillators of various design can be constructed which provide energy at several hundred to several thousand cycles per second. The Wein bridge phase shift oscillator was used for this purpose.

Since the oscillator is powered by batteries, there is no 60-cycle alternat-

ing current introduced inside the Faraday shield. It has been apparent that during the use of high-gain amplifiers an electrostatic shield surrounding the animal and preamplifiers is mandatory to eliminate interference from 60-cycle current radiated from power lines; this assumes additional importance in multiple recording.

The 0.002 μF capacitors of the Wein bridge (Fig. 1) were selected to

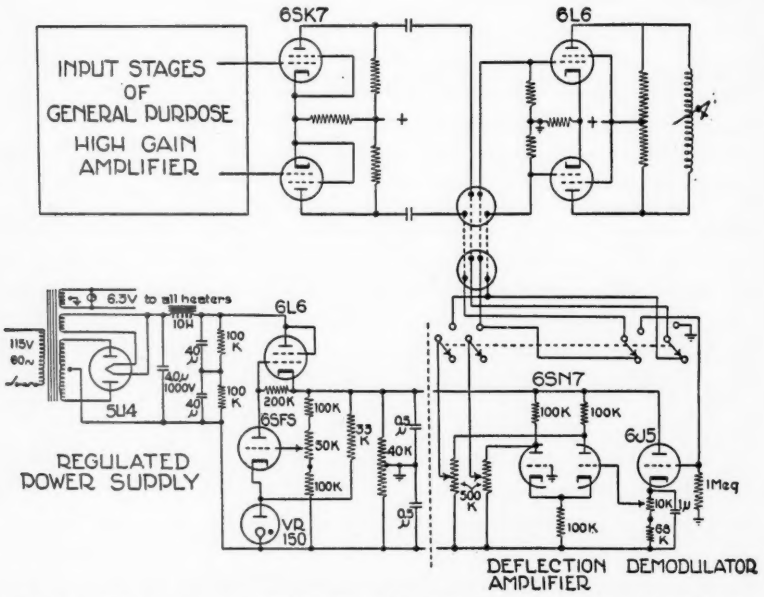

FIG. 2. Cathode follower demodulator with regulated power supply. The deflection amplifier and demodulator portions of the circuit must be duplicated for each channel. The switching circuit shown allows the EEG amplifiers to be used without demodulation when desired.

provide oscillation at about 800 c.p.s. The 150 K ganged variable resistor provides for some variation of the frequency. Additional frequency ranges may be obtained by changing the impedance of the bridge. The 3 K variable resistor is adjusted to provide maximal stability of oscillation and also to influence the shape of the wave. A 250 K potentiometer regulates the voltage output of the oscillator. The output, when not loaded, yields 22 volts r.m.s. A Wagner ground across the output is necessary to balance

multiple grounding effects. The entire assembly is enclosed in a metal box $5\frac{1}{2}'' \times 7'' \times 11''$. When the box is fitted with shielded cables, no oscillation is radiated to other channels during multiple recording.

Demodulator. Demodulation is accomplished by the use of an infinite impedance, cathode follower, detector (see Fig. 2). The 500 K balancing potentiometers move symmetrically about the zero voltage point and thus there is no distortion in the 6L6 stage. Balance is obtained by first setting the 10 K cathode potentiometer for zero grid potential of the 6SN7 deflection amplifier and then adjusting the balancing potentiometers until both sides of the output to the 6L6's are at zero potential. A high impedance vacuum tube volt-meter must be used. The 10 K potentiometer is ordinarily used to set the zero signal position of the oscillograph pens.

A switching system is provided so that the amplifiers may be used direct, undemodulated, when desired.

A well-regulated power supply for the demodulators is necessary to prevent variation in base line (no transducer signal) and so to permit reproducible calibration. Regulation for three channels is obtained by a combination of gas tube and electronic degeneration regulation as shown. It will be noted that in the 6L6 of this power supply, a potential difference of 300 volts exists between the cathode and heater. In heavy duty operation this may prove a source of difficulty and the use of a separate filament transformer is desirable.

Transducer for recording blood pressure. The recent development of the strain gage has provided a convenient device for the electrical recording of blood pressure.[2] The basis for the strain gage depends on a change in electrical resistance (ohmic) as an electrical conductor is lengthened or shortened. With the proper selection of wire, usually a cupro-nickel alloy, even a change of 1×10^{-6} inch will provide a measurable change in resistance. In measuring blood pressure, the strain gage is affixed (bonded) to a shim metal membrane or diaphragm of a pressure chamber and this in turn connected to the desired artery.* Blood pressure acting on the metal membrane will cause it to be distorted into an arc whose length is greater than the length of the membrane without applied pressure. The strain gage being bonded to the membrane undergoes a corresponding change in length and, in turn, resistance.

To measure this change of resistance, the strain gage is incorporated into

* It is obvious that these strain gages may be used in the measurement of any biological stress causing a mechanical movement; the pressure chamber is but a special application.

a balanced Wheatstone bridge. Any change in resistance of the gage upsets the electrical balance of the bridge and causes a current to flow in the output circuit which is detected by a galvanometer. In the multiple recording technique, the Wheatstone bridge incorporating the strain gage is powered by the Wein bridge oscillator, and the unbalance signal is increased by the amplifiers to a point where the pen recorder can be operated. Demodulation is used to remove the oscillator carrier wave.

The blood pressure recordings obtained are almost ideally isometric in character, as the application of 100 mm. Hg pressure to the chamber causes less than 0.5 mm^3 fluid displacement. The gage exhibits a linear relationship between applied pressure and resistance because the elastic limit of the wire is not exceeded. Because of the negligible mass of the strain gage it can respond faithfully to varying stresses with a frequency up to 30,000 c.p.s. Thus there is no distortion in the shape of the blood pressure pulse contour; the limitation rather occurs in the accessory apparatus—particularly the magnetic oscillograph pen motors. In practice, good reproduction of pulse pressures with a clear dichrotic notch is obtained, thus yielding more information than from the mean damped pressure recordings obtained from the usual mercury manometers.

Strain gages with attached pressure chamber, in ranges of 0-3 p.s.i. to 0-16 p.s.i., are available commercially. The resistance wire strain gage SR-4* may also be cemented to any desired pressure chamber.

Electrode transducer triode for general fluid pressure measurements. An alternate procedure for recording blood pressure activity involves the use of an electrode transducer triode. This tube, RCA developmental C 798-G,† is so constructed that its anode or "plate" passes through a thin metal diaphragm and is contiguous with an external shaft (Fig. 4). A displacement of this plate shaft changes the distance between the fixed grid and plate and results in a change in plate current. A movement of the plate shaft of $\pm$ 0.5 degree provides a 34 volt change (or 0.5 ma. change across the 65 K plate resistor). Inside the tube, the plate has a minimum free resonance of 12,000 c.p.s., thus permitting undistorted measurements of vibrations up to that frequency. In consequence there is no distortion of rapidly changing physiological phenomena, as e.g. pulse contours. For the isometric recording of fluid pressure activities, the plate shaft is connected via a link to the metal membrane of a pressure chamber, as illustrated in Figure 3.

* Baldwin Locomotive works, Southwark Division, Philadelphia.
† This tube has now been designated RCA-5734 triode transducer.

Using this method it is possible to measure pressures of 0-5 mm. H_2O. Cerebrospinal fluid pressure recordings using the *cisterna magna* or by lumbar puncture are easily obtained.

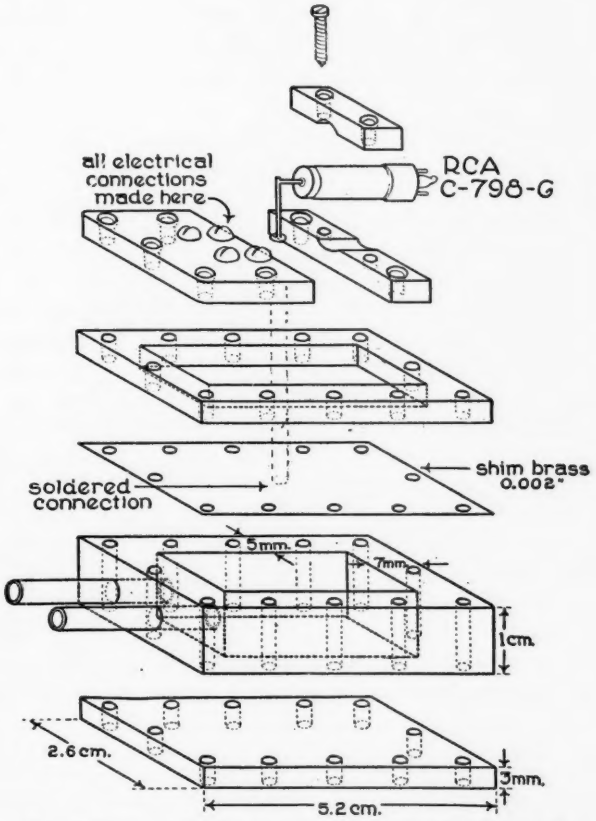

FIG. 3. Pressure chamber for use with RCA-C-798-G transducer triode. All parts were constructed of transparent plastic except the membrane and tubes for pressure connections for which brass was used.

The major advantage of this procedure over the strain gage technique is that a greater signal is obtained and less amplification to operate pen motors is required. In practice, only a single stage of amplification obtained

from the low microphonic 1620 pentode is used (see Fig. 4). The output can then be direct-coupled to the 6L6 stage which drives the pen motors. There is usually available a 'phone jack in the power amplifiers for monotoring with an oscilloscope, facilitating this connection. With the use of this direct-coupled system, no carrier current amplification system is required and the oscillator and demodulator are not needed.

In operation, the plate shaft should be grounded and the cathode

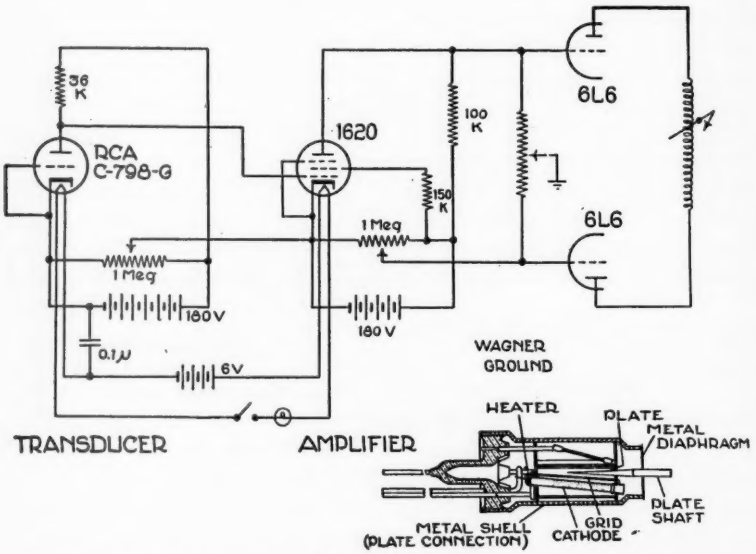

FIG. 4. Triode transducer amplifier circuit. *Insert*: cross sectional diagram of transducer triode.

operated at 180 volts below this ground potential. If this precaution is observed, the plate shaft does not connect battery voltage via the saline of the pressure chamber to the animal. The tube face should also be carefully protected against contact with saline; only brief contact with saline is required for electrolytic action to erode through the thin metal diaphragm destroying its vacuum.

Transducers for recording respiratory activity. Movements produced by the muscles associated with breathing can readily be transformed into electrical signals by a variety of means. A Piezo electric crystal from a

phonograph tone arm is mounted so that muscle motion acts on the needle receptacle of the crystal cartridge. A strain gage element or transducer triode may also be used. An additional example involves a ferrometal plate taped to the thorax which moves in the field of a magnetic ear phone. Such techniques, however, indicate only the frequency of inspiration and expiration and are inadequate measures of respiratory function as a whole.

Observations of tidal air exchange as well as respiratory frequency are sufficient indices of respiratory function because in most instances gas exchange values are constant. Recordings of the changing volume of air inside the chest may be obtained by measuring its changing electrical impedance. Since the dielectric constant for air is appreciably lower than that of the tissues, marked variations in electric impedance will occur between two electrodes placed across the chest cage. Whitehorn and Perl[13] measured the capacitance component of impedance by causing the changing capacity to shift the frequency of a resonant circuit oscillator and using an F.M. discriminator. We found it more convenient to measure the changing A.C. resistance of the chest. With copper gauze chest electrodes 3×6.5 cm., the A.C. resistance of the chest was found to be approximately 300Ω in rabbits and cats. A Wheatstone bridge was constructed using the animal's chest as one arm of the bridge. The power factor of the bridge was then approximately balanced for each animal, utilizing an oscilloscope to detect a null point. A 1000Ω variable resistor approximated the animal's mean A.C. resistance and one of a series of capacitors varying from $0.001\mu F$ to $0.1\ \mu F$ in ten steps was selected for balance also. The bridge was powered by the Wein bridge oscillator and the demodulator used. A Wagner ground was included.

In order to calibrate the impedance method, a Krogh spirometer was connected to a tracheal cannula. With a planimeter, the areas of the tracing of chest impedance for all the respiratory efforts of one minute were summed and compared with the minute volume obtained from the spirometer. If absolute respiratory volume measurements are desired, the calibration must be made for each animal because of varying shapes of the thorax with different animals.

An even simpler device for registering respiratory activity consists of a thermocouple inserted in the airway. The passage of air heated by the body during expiration causes a change in voltage of the bimetallic junction related to the extent and duration of expiration. On inspiration, cool air provides a similar disturbance. For most efficient operation it is obvious that a constant room temperature well below that of body temperature is

required. The use of such a thermocouple method provides a rough index of tidal air exchange. Though not precise enough for measurement of absolute tidal air exchange values, the method will easily detect changes in tidal air following drug action.

Thermocouples (iron—iron constantan) were made according to the

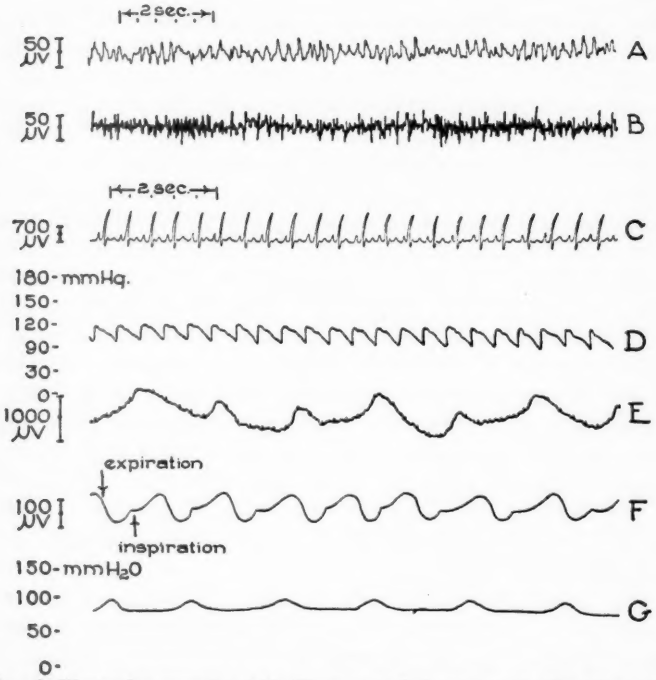

FIG. 5. Illustrative records: (A) Electroencephalogram, and (B) electromyogram (cat). (C) Electrocardiogram, and (D) blood pressure (dog). (E) Respiration (impedance) (rabbit). (F) Respiration (thermocouple) (rabbit). (G) Cerebrospinal fluid pressure (dog).

method of Riley.[10] The thermocouple was then inserted through the lumen of an airway. Small-cuffed Magill endotracheal tubes were used for dogs. With cats and rabbits, plastic tubing of suitable size (radio spaghetti) was found useful as an airway, and the mouth was packed with gauze to provide a loose seal.

Illustrative animal records. In Figure 5 are illustrated selected records

obtained using the various transducers described in this paper. Although these records were obtained from different animals, if sufficient amplifier channels are available, this is not necessary. The cortical electroencephalogram (A) was recorded in a cat anesthetized with pentobarbital sodium using needle electrodes driven into the exposed skull overlying approximately the cruciate sulcus; leads were connected to both grids of the amplifier. In the same animal, the electromyogram (B) is presented; an Adrian-Bronk coaxial electrode was inserted into a flexed triceps muscle. The electrocardiogram, lead II, (C) of a dog anesthetized with "Dial-urethane" was obtained in the usual manner. The blood pressure record (D) of this dog from a cannulated carotid artery utilized the strain gage and carrier current amplifier system and demodulation. Two rabbits anesthetized with pentobarbital illustrate the type of respiratory record obtained by the chest impedance (E) and thermocouple (F) techniques. It will be noted that EKG activity (shown as small spikes) is impressed on the respiratory tracings obtained with the impedance method. Lastly is presented the lumbar cerebrospinal fluid pressure record (G) of a dog anesthetized with pentobarbital sodium, as measured using the triode transducer. The blood pressure and cerebrospinal fluid pressure records were calibrated in the usual fashion by applying pressure while mercury and saline manometers were in the system.

The overall appearance of these records may prove somewhat unfamiliar because the speed of the recording paper is somewhat greater than that of the usual kymograph. In order to distinguish important aspects of the EKG, the paper speed should be about twice that illustrated. The records of respiratory activity and blood pressure would yield the same content of information if the paper speed were reduced less than that illustrated. Fortunately most electroencephalographs are equipped with paper pullers which have a selection of three or more speeds. It is possible to select a suitable paper speed at any time during the experiment.

It was found desirable to extend the length of pen arm of the oscillographs for the blood pressure tracings; an increase in accuracy of measurement of the pressure was thus obtained. Since this modification caused two neighboring tracings to overlap, different colored inks were used.

Summary

The standard electroencephalograph has been adapted for simultaneous multiple recording of electrophysiological and classical kymographic data.

A carrier current system and demodulator are described to adapt the amplifiers for blood pressure and respiratory tracings.

Transducer techniques are described to convert blood pressure, cerebrospinal fluid pressure, and respiratory activities into changes in electrical energy suitable for use with the amplifiers.

The authors are deeply grateful to Professor H. S. Burr for his kind co-operation and encouragement during the progress of this work.

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RELATION OF AMINO ACIDS TO TRYPANOCIDAL ACTIVITY OF PARASORBIC ACID*

B. A. RUBIN†

With techniques and materials previously described[5] a number of lactones (both naturally occurring and synthetic), and some related compounds, have been shown to have definite *in vitro* trypanocidal activity. It was further shown that these compounds have therapeutic effect *in vivo*.

The concept that specific chemical substances can interfere with the action of a chemotherapeutic agent provides an important starting point for the rational synthesis of biologically active compounds and the study of biochemorphology. Although the most important stimulus for this view came from the discovery of the striking relationship between PABA and the sulfonamides, there are many chemically unrelated substances which also interfere with sulfonamide activity. In fact, the earliest examples of drug antagonisms, between SH- compounds and arsenic or mercury, are clearly not between related chemical structures.

The present studies deal with an attempt to relate the recently discovered trypanocidal activity of a group of compounds (represented by a typical member of the group—parasorbic acid) to some known metabolic function.

Experimental

A method of approach was suggested by the structural similarity of the lactones and known "essential metabolites." It is evident that ascorbic acid is very similar in basic structure to the Δ^{2}-γ lactones. Ascorbic acid itself is somewhat toxic to trypanosomes, but a subinhibitory level had no effect on the trypanocidal action of parasorbic acid (δ hexenolactone). Similarly, pantolactone (α-hydroxy—$\beta\beta$-dimethyl—γ-butyrolactone) which sometimes acts as an adequate substitute for pantothenic acid,[7] is closely allied structurally to the saturated lactone group. In order to determine the relationship of pantothenic acid to lactone activity, calcium pantothenate and its components, pantolactone and β-alanine, were each added in various concentrations to an anti-trypanosomal titration of parasorbic acid. (Para-

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sorbic acid was used as the test lactone because of its effectiveness in a range where either inhibition or potentiation of effect could be readily detected and because it had been previously investigated with regard to its mechanism of action in other biological systems.) The results of this experiment are summarized in Table 1. It seems that β-alanine must exist in a free state, or in one unrelated to the structure of pantothenate, to exert its activity. It was evident that in this system neither the pantothenate nor the pantolactone had any effect at non-toxic levels.

TABLE 1

INFLUENCE OF CALCIUM PANTOTHENATE, PANTOLACTONE, AND β-ALANINE ON TRYPANOCIDAL ACTIVITY OF PARASORBIC ACID

Agent	% *Conc.*	*Dilution of parasorbic acid × 1000* 10*	20	40	80	160	320	0
		Effect on trypanosomes in 20 hrs. at room temp.						
Control (water)		0†	0	0	0	3+	4+	4+
Ca Pantothenate	0.27	0	0	0	0	0	0	0
Ca Pantothenate	0.10	0	0	0	0	+	4+	4+
Pantolactone	0.10	0	0	0	0	3+	3+	4+
β-alanine	0.10	0	0	3+	4+	4+	4+	4+
β-alanine	0.037	0	0	2+	3+	4+	4+	4+

* Dilution, one part in the number given.

† More than 100 organisms per low power field = 4+
10-100 " " " " " = 3+
1-10 " " " " " = 2+
.1-1 organism " " " " = 1+
Less than 1 " " 10 fields = ±
No viable organisms = 0.

These results substantially agreed with those of Hauschka,[4] and of Buston and Roy,[1,2] and their approach was followed in investigating the effects of related amino acids. A summary of the results obtained in tests with 24 amino acids is found in Table 2. It can be seen from this table that the amino acids fall into three indistinct groups. Some inhibit the trypanocidal effect of parasorbic acid, some have no effect, some potentiate its action. The reversing effect is most definite with β-alanine, glycine, and DL-glutamic acid. All the other amino acids have either no effect or a potentiating one. The most marked potentiating effect is seen with DL-norleucine, DL-threonine and α-amino butyric acid. Different concentrations

TABLE 2

EFFECT OF AMINO ACIDS ON TRYPANOCIDAL ACTIVITY OF PARASORBIC ACID IN VITRO AT 25° C. FOR 20 HOURS

Compound	*Concentration %*	*Inhibitory dil. of parasorbic acid (× 1000)*	*Ratio to control (+) potentiation (—) reversal*
Control	.....	80	.....
Glycine	.80—.40	40	(—) 2.0
	.20	20	(—) 4.0
	.10	30	(—) 2.7
	.01	40	(—) 2.0
β-alanine	.40	10	(—) 8.0
	.20—.10	15	(—) 5.3
	.04—.01	20	(—) 4.0
DL-alanine	.40	80	1.0
	.20	40	(—) 2.0
	.10—.01	80	1.0
Taurine	.20	80	1.0
	.10—.01	60	(—) 1.3
Aspartic acid	.10	120	(+) 1.5
DL-glutamic acid	.20	20	(—) 4.0
	.10	40	(—) 2.0
	.01	60	(—) 1.3
L-cysteine	.02	100	(+) 2.0
	.002	40	(—) 2.0
DL-serine	.10	60	(—) 1.3
DL-threonine	.20	320	(+) 4.0
DL-valine	.10	80	1.0
DL-methionine	.20	160	(+) 2.0
DL-(α)-amino butyric acid	.20	480	(+) 5.0
α-amino isobutyric acid	.20	160	(+) 2.0
DL-norleucine	.10	320	(+) 4.0
	.01	160	(+) 2.0
DL-leucine	.10—.01	160	(+) 2.0
DL-isoleucine	.10	80	1.0
Asparagine	.10	120	(+) 1.5
DL-lysine	.10	80	1.0
δ-amino valeric acid	.10	160	(+) 2.0
ε-amino caproic acid	.20	160	(+) 2.0
DL-(β)-phenyl-alanine	.10	160	(+) 2.0
DL-tryptophane	.10	60	(—) 1.3
DL-proline	.25	80	1.0
DL-hyroxy-proline	.25	160	(+) 2.0

NOTE: Controls containing only the amino acid were always run. Only in the case of .02% cysteine was there any effect on trypanosome growth.

of some amino acids were tested to determine changes in activity. The results of such a study are also presented in Table 2. Only β-alanine maintains a high level of lactone reversing effect over a wide range of concentrations. The effect of DL-alanine is the most restricted, appearing only at one concentration. The paradoxical effect of cysteine may be explained by the rather high toxicity of cysteine and other reducing substances for trypanosomes. A quantity of cysteine far less than its own inhibitory level shows the characteristic lactone reversing effect that is described by Cavallito and Haskell.[3]

TABLE 3

EFFECT OF COMBINATION OF AMINO ACIDS ON TRYPANOCIDAL EFFECT OF PARASORBIC ACID AT ROOM TEMPERATURE FOR 20 HOURS

	Parasorbic acid dilution × 1000						
	10	20	40	80	160	320	640
Amino acid	*Growth of T. equiperdum*						
Control (water)	0	0	0	0	3+	4+	4+
β-alanine 0.1%	0	±	2+	3+	4+	4+	4+
DL-norleucine 0.1%	0	0	0	0	0	0	2+
β-alanine 0.1% + DL-norleucine 0.1%	0	±	3+	4+	4+	4+	4+
L-glutamic acid 0.1%	0	0	+	3+	4+	4+	4+
D-glutamic acid 0.1%	0	0	0	0	0	+	3+
DL-glutamic acid 0.1%	0	0	+	3+	4+	4+	4+

The fact that amino acids both potentiate and inhibit suggested experiments in which agents representing each type of activity were used simultaneously in a parasorbic acid titration. The results of such experiments are summarized in Table 3. The data show that when a reversing and a potentiating agent are added simultaneously, the total effect is that of the reversing agent alone. Similarly the racemic mixture of an amino acid acts like the optical isomer which gives the reversing effect.

In order to ascertain a possible reason for the variations in reversing effect by β-alanine, the importance of time relationships was studied. Ordinarily, when the effect of an amino acid was tested on the trypanocidal activity of a lactone, both agents were mixed in a tube before the trypanosome culture mixture was added. However, when the reversing

agent was added first and allowed to remain in contact with the culture for some time before the trypanocidal agent was added, the final result was quite different. Typical experimental results of this kind are presented in Table 4. It should be mentioned that no such change in effect occurs when incubation time is similarly varied in the presence of parasorbic acid alone. The influence of increased time of contact with β-alanine is very marked, giving reversal effects exceeding those obtained by any concentration of β-alanine added in the usual manner.

The procedures followed in these experiments have been discussed in detail.[6] It should be noted that multiple controls were included in each part of each experiment. The separate toxicity of the test agents, as well as of

TABLE 4

INFLUENCE OF TIME RELATIONSHIPS ON REVERSING EFFECT OF 0.1% β-ALANINE ON PARASORBIC ACID ACTIVITY AT ROOM TEMPERATURE FOR 20 HOURS

	Parasorbic acid dilution × 1000				
	10	20	40	80	160
Amino acid	*Growth of trypanosomes*				
Control (water)	0	0	0	0	3+
β-alanine added at same time as parasorbic acid	0	±	+	3+	4+
β-alanine and culture in contact 3 hrs. before addition of parasorbic acid	+	2+	4+	4+	4+

the components of the medium, was always checked. The amino acids and the metabolites alone were without effect, with exceptions mentioned in the text. Tests were always done at least in duplicate, and always in at least two separate experiments (utilizing different batches of culture fluid). In Table 2, scoring was relative to the effective trypanocidal dose of parasorbic acid, which differed only very slightly among the different runs. The dilutions were two-fold, and in no case did any titration value differ by more than one dilution in separate experiments. Results presented here are averages of at least four tubes (for the less interesting agents) and in some cases are averages of 10-15 tubes, from 4-5 separate experiments. An average difference of up to two-fold in either direction may be of borderline significance, but anything greater can be considered reliably significant.

Discussion

In agreement with Hauschka's work,[4] it was found that cysteine and β-alanine did reverse the effect of parasorbic acid. Alpha alanine was found to have a much less reversing effect than Hauschka claimed, but our findings agreed with those of Buston and Roy.[1,2] And contrarily, it was found here that glycine and DL-glutamic acid also reversed the activity of parasorbic acid while Hauschka found that they potentiated its effect. The results obtained by mixing inhibiting and potentiating agents and delaying the addition of the lactone seem to indicate a type of competitive enzyme inhibition. Some amino acids may sterically block the approach of the parasorbic acid and potentiating agents, but not of the normal substrates. Such mechanisms involving amino acids have recently been discussed in great detail.[7]

Summary

The mechanism of trypanocidal activity of lactones was sought in metabolite antagonism, using ascorbic acid and calcium pantothenate. Neither of these had any effect, but in testing portions of the pantothenate moiety, β-alanine was found to inhibit the activity of parasorbic acid. Twenty-four amino acids were then tested in lactone-trypanosome systems and found to fall into three, not sharply defined groups—those which potentiated, those which inhibited, and those which had no effect. When an inhibiting and potentiating agent were both added, only the effect of the former was seen. When a lactone inhibitor was incubated with a susceptible organism, the effect of the lactone (added later) was reduced much beyond the expected level.

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DIARRHEA IN THE OTHERWISE HEALTHY INFANT*

ARTHUR S. BRACKETT

There is a group of otherwise healthy infants who have diarrhea of non-infectious, unknown etiology in the early months of life. These cases are generally mild and have been considered benign, though sometimes they become serious because of undue loss of water and electrolytes. This article is to consider what effect the size of the feedings has on otherwise healthy babies who have watery and frequent stools. In earlier studies of vomiting and colic,[2] I was impressed to find that treatment based on improving the mechanics of digestion helped, and in most cases cured, both vomiting and colic. Furthermore, the same treatment stopped diarrhea in many otherwise healthy babies.

In a study of these cases diarrhea was found to be alleviated or cured by the treatment described earlier, i.e., small, concentrated, frequent feedings. It is also possible to use these principles of treatment on babies sick with pneumonia, virus diseases, respiratory infections, etc., when their illness is complicated by diarrhea. In many instances the cause of the diarrhea is obscure. I have no doubt that mild cases may occur from different kinds of bacteria and viruses; allergic reactions of the intestinal tract may be involved, while other cases may be due to causes still unknown. But I am convinced that there are cases, generally mild, but sometimes severe if wrongly diagnosed and treated, which follow the giving of large, dilute feedings. Possibly because of some abnormality of structure or function of the ileocecal sphincter and/or the large intestine, the colon is unable to handle the large feedings, and diarrhea results.

Frequency of cases and their treatment. Conclusions are based on the case histories of 195 babies seen in private practice, at a well-baby clinic, and at a hospital where a few of them had been sent as feeding problems. Of these 195 cases there were the following: (i) with diarrhea, 68 babies; (ii) without diarrhea, 75 babies; (iii) histories incomplete, 52 babies. Probably this series shows a higher percentage of diarrhea than would be found in the general infant population, though I am confident that mild cases occur more frequently than is generally recognized. It should be

* The term diarrhea is here defined as the condition arising when there are at least three watery stools a day.

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remembered that most of these babies are not sick; they probably have digestive tracts which *mechanically* do not function well.

Results of treatment were gratifying. Whenever I have received cooperation from the parents, the results have been satisfactory. The chief obstacle encountered was failure on the part of the mother to carry out directions, due to the almost universal belief that any crying is caused by hunger. In a few instances where the mother was unintelligent or uncooperative and thought it too much bother to give frequent feedings, the result was unsatisfactory.

Case histories

Case 265. Six weeks old when first seen. History of regurgitation in early weeks, followed by colic from four to six p.m. Birth weight, 7 pounds, 4 ounces, weight at six weeks, 9 pounds, 9 ounces. Had not gained for the previous two weeks, having six watery stools a day. Had been taking

Evaporated milk	12 oz.	5 feedings,
Water	18 oz.	6 oz. per feeding
Dextri-maltose	4 T	

Formula was changed to

Evaporated milk	10 oz.	5 feedings,
Water	12 oz.	4 2/5 oz. per feeding.
Dextri-maltose	4 T	

In a week the baby gained 7 ounces, having two or three stools daily. Note that the bulk of food was reduced about 26% and the caloric value 16%.

Impression: Probable small capacity of the large intestine.

Case 259. When first seen, this baby had been having six watery stools a day on

Evaporated milk	13 oz.	7 feedings,
Water	26 oz.	5 4/7 oz. per feeding.
Dextri-maltose	6 T	

Formula was changed to

Condensed milk	4 oz.	7 feedings,
Water	20 oz.	3 3/7 oz. per feeding.

In a week he gained 12 ounces and the stools became pasty and less frequent. Note that the reduction in bulk was about 40%.

Impression: Large intestine had been incapable of absorbing the larger quantity of water and electrolytes and thus had to hurry along the contents still in a fluid state.

Case 106. When first seen she was 43 days old, having regurgitation, colic, and frequent loose green movements. In the 43 days had gained only 12 ounces. Had been on

Pasteurized milk	16 oz.	6 feedings,
Water	8 oz.	4 oz. per feeding.
Cartose	3 T	

We think of stools as green, yellow, gray, watery, loose, pasty, large, small, smooth, etc., but never in terms suggesting the force causing defecation. In my presence, while

the mother was changing a diaper on a table, a stool was ejected 4½ feet (actual measurement), showing how high must have been the intra-abdominal pressure. Probably the civilized diaper covers many cases of projectile defecation.

Formula was changed to

Evaporated milk	9½ oz.	10 feedings,
Water	9½ oz.	1.9 oz. per feeding.
Karo	2 T	

Three days later, no regurgitation, colic improved, only two pasty movements a day. Since colic persisted, changed to

Olac	10½ T	10 feedings,
Water	12 oz.	1.2 oz. per feeding.
Karo	1 T	

Colic ceased. In ten days, after first change of formula, the baby gained 14 ounces. Regurgitation and projectile vomiting stopped concomitantly with the diarrhea and projectile defecation, suggesting that the stomach and colon act alike in getting rid of too large a volume.

Case J. E. This baby had had colic and frequent stools for three weeks. When first seen he was on

Skim milk	22 oz.	5 feedings,
Water	9 oz.	6 1/5 oz. per feeding.
Karo	2 T	

Formula was changed to

Evaporated milk	9 oz.	10 feedings,
Water	9 oz.	1.9 oz. per feeding.
Karo	2 T	

The number of stools dropped immediately to two a day and colic ceased. (The father gained five pounds in a week!) Almost three years later the mother reported that the child still preferred five small meals a day to the usual three.

Case 25. Ten days old when first seen. Had had vomiting, colic, and diarrhea. Was on a Biolac mixture of 4 ounces every 4 hours. Was put on evaporated milk and water, half and half, 10 feedings daily, 1 3/5 ounces per feeding. Vomiting, colic, and diarrhea all ceased in a few days.

Case 55. Had had vomiting, colic, and diarrhea, which all ceased when given feedings of 1 7/10 ounces every two hours. When mother tried giving 2 ounces per feeding, all three troubles recurred. Child had no trouble when returned to 1 7/10 ounces every two hours.

Case 96a. This was an older brother of case 96b. He had had colic and diarrhea for five weeks according to history obtained from mother. Was still a nervous child.

Case 96b. Was 18 days old when first seen. Had had diarrhea since leaving the hospital. Was on

Grade A milk	18 oz.	6 feedings,
Water	6 oz.	4+ oz. per feeding.
Cartose	2½ T	

Formula was changed to

Evaporated milk	8 oz.	8 feedings,
Water	8 oz.	2 1/8 oz. per feeding.
Karo	2 T	

In two or three days diarrhea and colic ceased. In eight days gained 13 ounces. Note that both siblings had diarrhea.

Impression: Small colon (perhaps hereditary).

Case 254. Five months old when first seen. Birth weight, 7 pounds, 5 ounces. No vomiting, but had had diarrhea for two months and was somewhat dehydrated. Was on

Pasteurized milk	22 oz.
Water	8 oz.

Because the baby cried and sucked his thumb, the mother thought he was hungry and made up the formula twice a day! These 60 ounces were given irregularly in approximately 10 feedings a day. Stools were green and watery, from 10 to 15 daily. Changed to

Condensed milk	6 oz.	7 feedings every 3 hours,
Water	25 oz.	4 3/7 oz. per feeding.

In a few days baby was having only two stools a day and gained 19 ounces in a week. Mother's report: "a different baby."

Impression: Overfeeding per feeding (and probably a small colon).

Case 298. Two months old when first seen. Had regurgitation, occasional projectile vomiting, colic, and diarrhea. Had been on

Evaporated milk	13 oz.	no regular schedule,
Water	7 oz.	size of feedings varied,
Dextri-maltose	4 T	was losing weight.

The mother was worn out so baby was placed in hospital. Formula was changed to

Condensed milk	5 oz.	10 feedings,
Water	21 oz.	2.6 oz. per feeding.

Within two days baby had occasional regurgitation, but no projectile vomiting nor colic, and only two formed stools daily. In ten days he gained 25½ ounces.

Discussion

The caloric needs of the infant should be determined as exactly as possible. Many mild cases of diarrhea can be alleviated by dividing the 24-hour ration into 7 feedings instead of 6, with about a 14% reduction in bulk in each feeding. Other more severe cases have been cured simply by reducing the volume of water, sometimes cutting it in half, leaving the caloric value the same. For example:

Evaporated milk	8 oz.	6 feedings,
Water	16 oz.	4 1/6 oz. per feeding.
Karo	2 T	

Changed to:

Evaporated milk	8 oz.	6 feedings,
Water	8 oz.	2 5/6 oz. per feeding.
Karo	2 T	

This gives approximately a 30% decrease in volume with the same caloric value.

If a case is severe enough to require a division of the bulk into ten feedings, there is approximately a 59% reduction of bulk, with the same caloric value. If condensed milk is used (which provides 126 Calories per ounce) and the caloric needs of the infant are figured at 50 Calories per pound, an 8-pound baby requires slightly over 3 ounces of condensed milk. In severe cases condensed milk should be diluted 1 to 4 with water, the formula being divided into 7 to 10 feedings according to the severity of the case.

Water should be given between meals, especially in hot weather.

These cases have been treated at the homes almost entirely. In very few of my cases has it been necessary to send the baby to the hospital.

Sequelae. The importance of stopping mild cases of diarrhea, often ignored by the profession, is evident when one realizes that the consequences may be more serious than the original trouble. The most frequent complications of the diarrhea of early infancy are those of the urinary tract and skin. Pyelitis and its complications are present in 1% of all hospitalized children. Helmholz[8] says that pyelitis is six times as frequent in girls as in boys during the first two years of life; after the second year, three times as frequent. It is found most often in girls of the diaper age, and its frequency in girls is thought to be due to the anatomy of the parts. Eighty per cent of the cases are infected by bacilli of the colon-aerogens group from the feces. Since frequent, watery stools seem likely to transfer colon bacilli to the urethra, snugly applied diapers should be avoided when diarrhea is present. Watery stools in wet diapers are likely to macerate the skin, especially when rubber pants over the wet diapers discourage frequent changes of diapers. Ammoniacal dermatitis is due to the bacterium ammonigens in the feces, acting on urea in the urine to produce ammonia, a cause of dermatitis of varying intensity. Especially in fat babies with deep creases there may be an increased tendency to dermatitis when the stools are watery. Case 121 was operated on for a rectal abscess at the age of one month.

Prolapse of the rectum may be due to diarrhea.

The ileocecal sphincter and colon. The ileocecal sphincter, like the oral, pyloric, and anal sphincters, varies in its anatomy in different babies.

Authors speak of some ileocecal sphincters as being "tight," others "loose." The major function of the sphincter is thought to be the holding back of the flow of chyme into the cecum. As Alvarez[1] says, "If it were not for the ileocecal sphincter, nutrition might suffer and men and women might more often be bothered by diarrhea." Presence of food in the stomach causes a relaxation of the sphincter and passage of chyme into the cecum. This is evident when the stomach is overloaded with milk or when the milk is diluted with too much water, and may be a factor in the origin of this benign, mechanical type of diarrhea, as well as in the successful treatment of the diarrhea by using small, concentrated, frequent feedings. Since they must be small, it is necessary that the feedings be given concentrated and frequently, with as little water as possible, so that adequate calories may be supplied.

As is well known, the surgical ablation of a large portion of the colon causes diarrhea. In a personal letter, Dr. Francis E. McDonough[5] writes that "Diarrhea usually follows removal of large portions of the ileum and the right colon." From the report of Henderson and Briant[4] it is evident that the colon of healthy newborn infants varies much, both in length and lumen. It would be interesting and instructive if a series of infants with diarrhea of the type described here could be examined roentgenologically to determine whether they show constant variations from the average colon. In my opinion such a study would probably reveal that a baby with a short colon or with a small colonic lumen would have diarrhea more often than the average baby. It might even be possible to detect four different types of abnormality, as follows:

1. Infants whose colon is too small to absorb the contents rapidly enough to supply to the body the necessary water and inorganic salts.
2. Infants with a normal colon into which has been poured too large a bulk of chyme, the feeding being more than necessary for caloric requirements.
3. Infants with a colon too small who also are given feedings excessive in size, i.e., more than necessary to meet caloric requirements.
4. Infants who have an ineffective ileocecal sphincter.

To summarize, then, the colon, to function properly, must be large enough to provide sufficient surface, with cells endowed with the ability to pick up water and electrolytes, and its motor apparatus must not pass the contents along so fast that they are ejected still in a fluid state. Results are better when there is a steady, even flow, without the severe contractions which push the contents along at an accelerated pace.

Summary

There are a number of otherwise healthy infants, a larger number than is realized, who have diarrhea which may be prevented by giving small, concentrated, frequent feedings. This diarrhea is thought to be a consequence of the congenitally small capacity of the large intestine. An inefficient ileocecal sphincter is probably sometimes a factor.

In all the literature which I have seen, there has been no previous mention of the optimal size of the individual feeding in the treatment of diarrhea.

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DEVELOPMENTS IN ELECTROENCEPHALOGRAPHY: THE BASAL AND TEMPORAL REGIONS*

PAUL D. MacLEAN

In recent years developments in the fields of anatomy, physiology, and electrophysiology (of which electroencephalography is a part) have directed interest to the "down-under" and mesial parts of the cerebral hemispheres. In these regions, and surrounding the corpus callosum, lies that part of the brain called the limbic lobe by Broca. It was renamed the rhinencephalon by Turner because of its supposed olfactory function.† Contrary to this accepted belief, Papez proposed the theory in 1937 that the rhinencephalon was fundamentally concerned in both the experience and expression of emotion.[35] Since then there has been much experimental work to substantiate his theory (cf. MacLean[29] for review and references). Bilateral ablations, for example, in various parts of the rhinencephalon will, depending on the area involved, produce profound changes in the affective behavior of the animal. These range in degree and quality from rage and attack to placidity and tameness. On the other hand, stimulation experiments have shown that a wide variety of autonomic responses, commonly seen as the accompaniment of affective states, can be elicited from the entire anterior part of the rhinencephalon. It is startling to learn that many of these observations—involving both ablation and stimulation—were made during the latter part of the last century by Ferrier, Schäfer, Horsley, Brown, and others,[41] and are only now being rediscovered.

The rhinencephalon, which phylogenetically is the old part of the cerebrum, could justifiably be referred to as the primitive forebrain. This would help to counteract the impression that it has mainly to do with the function of smell.

In electroencephalography the search for focal abnormalities in cases of epilepsy, suspected tumor, psychiatric disorders, and other conditions has led to an exploration of those few accessible areas at the base of the brain where the primitive forebrain, and the phylogenetically newer cortex

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† The rhinencephalon embodies the posterior orbito-mesial part of the frontal lobe, the insula, the cingulate gyrus, and the hippocampal formation. On a comparative neuroanatomical basis, the hippocampal formation may be considered to include, besides the hippocampus, the amygdala and the hippocampal and dentate gyri.

associated with it, impinge on the wall of the cranium. It is the purpose of this review to summarize some of the findings that have come out of this work, and to indicate how they contribute to the understanding of the function of those parts of the brain under consideration.

Techniques for recording the bioelectrical activity at the base of the brain. The limitations of electroencephalography are generally not recognized by those outside the specialty. Contrary to what might be supposed, an electrode placed on the scalp over a limited area of the brain can give little specific information about the bioelectrical activity of the nerve cells in that region. Since the head is a volume conductor, the potential at an electrode on the scalp is influenced by the activity of brain cells at a distance as well as those directly underneath. Consequently it sometimes happens that one may believe one has established a focus of activity under a particular electrode, when in reality the disturbance has originated in a remote area. Moreover, it might be pointed out that though the electrode is separated from the brain only by a thickness of skull and scalp of about a centimeter and a half, this results in a great reduction in the size of the potentials that can be recorded from the surface of the head. The electroencephalographer is a little like the man who stands outside a banquet room and tries to interpret the multitude of noises and conversations that emanate from within.

The foregoing limitations do not begin to cover the problems facing the electroencephalographer. But they have been cited to indicate the special difficulties involved in recording the bioelectrical activity at the base of the brain, where, in contrast to the outer convexity of the skull, one's attempts at accurate localization are even more restricted because of the few electrode placements that are possible.

In the early days of electroencephalography there was only one position at the medial basal region from which recordings were made. In 1938 Grinker described an electrode with a sharp tip which, after passage through the nose into the nasopharynx, pierced the periosteum of the sphenoid bone.[10] Subsequently Schwab,[48] Greenblatt *et al.*,[9] and Umlauf[48] made various modifications of such an electrode which circumvented the piercing of tissues in the nasopharynx. Schwab's electrode was held in place by an inflated balloon. The electrode of Greenblatt *et al.* was simply an applicator stick to which a metal tip and lead-off wire were attached. Umlauf devised an electrode made of a rubber catheter with a solder tip; the electrode was stabilized in the nasopharynx by filling the tube with mercury.

It was formerly supposed that the nasopharyngeal electrode recorded the

activity of the hypothalamus.* But such an electrode when placed in the vault of the nasopharynx is probably four to five centimeters from the hypothalamus and is much nearer, and practically equidistant from, the anterior mesial aspects of the temporal lobes and the pons. As Jasper[18] and others have pointed out, such an electrode provides at best a "diffuse" lead.

In 1948 Roubicek and Hill, seeking to obtain a clearer definition of the electrical activity at the base of the brain, inserted wires through each side of the nose into the nasopharynx, and recorded the potential differences between them.[40] That same year, MacLean, working in Schwab's laboratory, devised a simplified form of the nasopharyngeal electrode which was also introduced through each nasal passage into the nasopharynx for bipolar recording.[28] It was demonstrated that such an electrode could be inserted in a matter of seconds without the use of a head mirror or nasal speculum and did not require the previous cocainization of the nasal passages. The electrode was bent in such a way as to allow the recording tip to come to rest in the posterolateral part of the nasopharynx. In this position each electrode is about two centimeters from the anterior mesial aspect of the temporal lobe on the corresponding side. The electrode is probably closer to this region of the primitive forebrain than to other parts of the brain. Experience in making hundreds of recordings has shown that the tracings obtained with these electrodes will usually measure up in quality to those from the scalp. Indeed, as the methods of recording from the nasopharynx have improved, it has become increasingly clear that many of the bioelectrical phenomena previously described as arising from the basal structures were artefact.

Subsequently, Arellano, also working in Schwab's laboratory, added to the scope of basal recording by devising an electrode which could be placed without anaesthetic into each auditory canal against the tympanic membrane.[1] This is made possible because the recording tip is a small ball of felt soaked in saline. The tympanic electrode is about one-half to three quarters of a centimeter from the inferior surface of the temporal lobe and in the neighborhood of the inferior temporal and fusiform gyri.

There are, of course, other anatomical sites at the base of the brain that are accessible to the placement of electrodes. Greenblatt *et al.* have described an ethmoid lead.[9] At the Neurological Institute in Montreal a technique has been worked out which allows recording from an insulated needle inserted against the periosteum just above the foramen ovale.

* It would be possible to probe the sphenoid sinus and thus place an electrode nearer the hypothalamus.

But it has not been generally recognized that an electrode placed on the ear lobe provides an excellent lead from the inferolateral and basal parts of the temporal lobe. The electrical activity from this part of the brain is characteristically of low voltage. This contributed to the mistaken inference that an electrode placed on the ear lobe is so remote from the brain as to be, for all practical purposes, "indifferent." As a result the ear lobe, or the ear lobes connected together, have commonly been used as an "indifferent" reference for so-called "monopolar" recording from the scalp. Such practice has led to errors of interpretation and failure to localize certain temporal lobe abnormalities.

In 1948 Arellano and MacLean reported a practicable method for recording the electrical activity across a limited area at the base of the brain by the use of two nasopharyngeal, two tympanic, and two ear-lobe electrodes.[8] These six "active" electrodes allow a series of five linkages for bipolar recording from the base. For so-called "unipolar" recording these electrodes may be referred to some remote and "indifferent" point such as the region of the sixth cervical vertebra.[30] The combination of both bipolar and "unipolar" recording greatly facilitates the localization of various bioelectrical phenomena. The foregoing method has been successfully employed in recording the basal electroencephalograms of a great number of patients, including children, elderly and feeble individuals, and psychotics.[31]

The basal and temporal regions in "psychomotor epilepsy." Psychomotor epilepsy derives its name from the work of Gibbs, Gibbs, and Lennox who in 1938 were the first to describe what they considered to be a characteristic electroencephalogram in patients suffering from seizures manifested by "psychomotor disturbances of a surly, unpleasant sort," "involuntary, tonic movements," and subsequent amnesia for their bizarre behavior.[7] The disease has also been referred to as "epileptic automatisms" by Penfield.* This form of epilepsy, which has protean manifestations, was described in detail by Hughlings Jackson in a series of papers that appeared during the last twenty years of the last century.[14] The seizure frequently begins with one, or a combination, of a great variety of sensory auras. With or without this aura there may be rather elaborate feeling or psychical states. Subsequently the patient may manifest staring, muttering, masticatory or other aimless movements, local or generalized tonic spasms of the limbs and body musculature, and bizarre, pseudopurposeful behavior for which he usually

* That several designations are used for this form of epilepsy is evidence that none of them is satisfactory.

has amnesia. Attacks may be very minimal and short lasting or continue for a considerable period; they may develop into generalized convulsions.

In their paper of 1938, Gibbs, Gibbs, and Lennox stated: "These interesting, but disconcerting, psychic episodes accompany cortical action potentials which are of high voltage and slow frequency—from 3 to 6 per second. There are a series of regular, square-topped waves. . . . The appearance is that of a positive potential which occurs at a rate of from 3 to 6 per second on an otherwise normal rhythm." They referred to this kind of electroencephalogram as the "psychomotor type."

In 1941 Jasper and Kershman showed that the so-called psychomotor pattern of the foregoing investigators was frequently accompanied by a focal discharge in the temporal lobes or subjacent structures.[17] In the latter instance they inferred that the discharge was "probably in the archipallium," for example, in the "hippocampus."

In 1948 Gibbs, Gibbs, and Fuster, following up a series of previous reports, summarized the findings in a study of 300 patients whose electroencephalograms showed "a psychomotor type of discharge."[8] They stated that a "spike focus" could be localized in every case to "the anterior temporal area on one or both sides." Ninety per cent of these patients had "a history of clinical psychomotor seizures." The authors again made the significant observation that the focus could be most readily demonstrated in natural or induced sleep.

MacLean and Arellano have recorded the standard and basal electroencephalograms of 24 selected patients with epilepsy.[20] The basal electroencephalogram was of particular interest in those cases with a history of automatisms. In this group spike activity was present in ten instances and could be localized to the temporal or basal regions.* In seven instances the origin of the spike activity appeared to be nearer the electrodes at the base than at the scalp. One nasopharyngeal electrode or the other was predominantly involved in six cases. In the remaining case where the localization was made at the base, the right tympanic electrode appeared to be nearest the focus. The tendency for the spike activity to occur bilaterally characterized the electroencephalograms of six patients. The authors noted that of all electrodes currently applied to the outer cranium, the nasopharyngeal and tympanic lie nearest "the basilar parts of the rhinencephalon," and emphasized that such anatomical considerations must be

* Previous routine electroencephalographic examinations had failed to show any focus in the majority of these cases.

taken into account in inferring the origin of the spike activity in the majority of the group of cases studied by them.

In a recent paper, now in press, Jasper has stated that in those cases of epileptic automatisms where an epileptogenic focus can be demonstrated at operation, the majority of such foci are in the vicinity of the tip of the temporal lobe, the island of Reil, and the adjacent gray matter extending into the uncinate region.[19] There are exceptional cases where the focus is in the mesial frontal or the posterior temporal regions.

The tendency for a spike focus to occur bilaterally in psychomotor epilepsy has been repeatedly described.[6, 17, 30] MacLean and Arellano have commented upon the possible mechanisms that might explain such phenomena.[30] Among the various possibilities they gave emphasis to the fact that many injuries and disease processes frequently affect both sides of the basal structures of the brain. They restated the long-known observation that the cells of Sommer's sector of the hippocampus show especial susceptibility to anoxia, hypoglycemia, a variety of infections, circulatory deficiencies, etc.[46] They suggested that such conditions may have been of etiological significance in the majority of the cases they reported.*

In recording the electroencephalogram of some patients during an automatism, Jasper has noted the onset of suppression of the bioelectrical activity of the brain when the patient begins to stare.[19] Hill has analyzed the electroencephalograms of 24 patients which were recorded during psychomotor seizures.[18] The seizure characteristically begins with a generalized depression of the cortical activity lasting a few seconds. This stage is followed by "rhythmic" activity of six to eight cycles per second which appears symmetrically in both hemispheres, and which is usually first seen in the frontal regions. During the next minute or so the frequency progressively falls to about two cycles per second, after which there is low voltage, very slow and irregular activity in all regions. Electroencephalograms of this variety are accompanied by the loss of consciousness

* Spielmeyer attributed the sclerotic changes in the hippocampus of many epileptics to the circulatory deficiency resulting from the convulsion.[46] Scharrer has observed that in the rakelike pattern of the vascular system of the hippocampus the blood pressure can drop locally below a critical level before this condition occurs in the rest of the brain.[42] Zimmerman concluded that "cerebral anoxemia" resulting from severe convulsions could account for the lesions in the hippocampus and other parts of the brain.[58] Whatever the mechanisms, it is possible to conceive how primary or secondary disease in the hippocampal formation might lead to a vicious circle whereby impaired brain cells in this region could trigger a convulsion that would contribute to further injury and a repetition of the morbid process. It would be worth while to reinvestigate what such a chain of events in the hippocampal formation might play in the intellectual and affective deterioration of the epileptic.[46]

and a transient generalized tonic spasm of the musculature. When such a discharge is unilateral, there is no loss of consciousness, and the patient may have psychical experiences which he can subsequently recall.

Along with the electroencephalographic findings all the foregoing papers have considered in some detail the symptomatology of epileptic automatisms. Little has been added to the description of the disease that was not noted by physicians in the last century. Save for the history and the electroencephalogram, extensive clinical investigation will uncover few findings in the vast majority of patients that point to focal disease in the brain.[5, 30] Indeed, it is very often only a scrupulous attention to the symptomatology in these patients that promotes the insistence on repeated electroencephalographic examinations (including "activation" and basal leads) for tracking down epileptogenic foci. The importance of making a localization arises from the fact that surgery may offer some help to these patients after all other measures fail.*

Further emphasizing the significance of the history is the observation that minor aberrations of psychomotor epilepsy are not infrequently diagnosed and treated as "petit mal," whereas seizures that progress into generalized convulsions may be considered "idiopathic." Only by more careful attention to the history are such mistakes to be avoided. The aura, for example, which is such a common feature of psychomotor epilepsy is characteristically absent in petit mal, as well as in most of those exceptional cases where automatisms are associated with epileptogenic foci in the frontal lobes.[19]

The great variety of auras and other symptoms occurring in psychomotor epilepsy should not be so bewildering as they are illuminating of the functions of the parts of the brain under discussion. Of considerable interest is the fact that practically every form of sensory aura—visceral, gustatory, olfactory, visual, auditory, somesthetic—has been described in cases of epileptic automatisms.† Associated with these various sensations, or occurring alone, may be feelings of fear or horror, expressions of anger, or psychical experiences, ranging all the way from indescribable feelings, dreamy states, feelings of familiarity, unreality, déja vu, etc., to frank hallucinations. Masland and Lockhart have paid particular attention to the great variety of subjective symptoms encountered in their study of 40 cases

* Of all patients subject to epilepsy, those with psychomotor seizures are least helped by anticonvulsant medication.

† Penfield has described a patient with a lesion of the temporal lobe who exhibited sexual ideas as a component of his dreamy state.[37]

with temporal lobe abnormalities, obtaining the patient's verbatim description of his feelings by sound recordings.[33] The reader is also referred to papers by Kershman[23] and O'Leary and Fields[34] which include cases with temporal lobe foci and a distinctive type of symptomatology.

Gibbs *et al.*[8] and MacLean and Arellano[30] have commented on the high incidence of psychiatric disorders that are present during the interseizure period of patients with psychomotor epilepsy. The manifestations include nervousness, irritability, stubborn, "fractious" behavior, rage states, somnolence, obsessive thinking, depression, schizoid reactions, disorders of memory, etc.

MacLean and Arellano have given emphasis to the convulsive visceral and autonomic phenomena associated with psychomotor epilepsy,* as well as to the tonic spasms of the extremities and body musculature, and have commented on their possible anatomical and physiological significance.[30] It was noted that the basilar parts of the frontal and temporal cortex, as well as the insula, are intimately related anatomically "to the phylogenetically oldest structures of the rhinencephalon," and that it was therefore conceivable that discharges in any of these regions might lead to similar epileptic manifestations. Not included in their discussion was reference to the so-called "second" motor and sensory areas which are in part adjacent to and partly included in the insular and temporal lobes. There is some evidence for believing that these so-called "second" areas represent a phylogenetically older sensory and motor cortex, developing out of the primitive forebrain.† It is possible that some of the bilateral sensory and motor manifestations of automatisms may result from the involvement of these regions in the epileptic discharge.

Tumors of the temporal and basal regions. Tumors involving the regions under discussion are capable of producing all the symptoms seen in association with psychomotor epilepsy.[6, 14, 20, 25, 26] As a rule, tumors present unsatisfactory material for studying localization of function in the brain because they involve or impinge upon so many different neuronal systems. In view, however, of the increasing interest in the role of the primitive forebrain in affective behavior the author would like to draw attention to

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* For example, the ictal vomiting, urination, flushing, pallor, cyanosis, shivering, etc.

† It is interesting that in such primitive forms as the opossum, bilateral movements can be obtained from unilateral stimulation of its motor cortex,[39] and that part of the excitable cortex is granular as well as agranular. Sugar *et al.*, also on occasion obtained bilateral movements from stimulating the "second" motor area in the monkey[47]; as in the opossum, the excitable areas included cortex of a granular type. In some cases contralateral movements continued for several minutes after cessation of the stimulus.

a striking case reported by Vonderahe.[49] The patient was a 17-year-old girl who suffered from epilepsy. As her illness progressed she developed a tendency to attacks of anger which became so severe that members of her family became fearful of being harmed. She died suddenly in status epilepticus. "Post-mortem examination . . . revealed a tumor, the size of a cherry, on the anterior and inner aspect of the left temporal lobe, where it encroached upon the amygdaloid nucleus and adjacent portion of the hippocampus."

Hill, in a paper on the electroencephalographic concept of psychomotor epilepsy, has stated: "In cases with intracranial neoplasm, the EEG pattern, if abnormal, usually showed a well-marked irregular slow wave focus which possibly masked the spike discharge if this was present. In fact, in only one patient with glioma of the temporo-frontal regions was a spike focus encountered without gross slow wave activity."[32]

The basal leads may be helpful in localizing tumors in the basal and temporal regions.[3] It is disconcerting, however, to encounter an occasional case with a proved large tumor in the temporal region where, despite attempts at activation and the use of special leads, no diagnostic abnormality can be demonstrated.

In cases of pituitary tumor the basal electroencephalogram characteristically shows little if any abnormality that can be detected by visual inspection. The use of an automatic analyzer,[51] however, may reveal the presence of 6 per second activity indicative of a deep disturbance.[40, 81] (See also Walter and Dovey.[80])

Behavior disorders. With the exception of the behavior disorders, there is little agreement in the literature as to the incidence of abnormalities of the electroencephalogram in various psychiatric conditions. And in reports generally there has been little attention paid to the localization of abnormalities when present.

In 1938 Jasper *et al.* analyzed the electroencephalograms of 71 "behavior problem children."[35] They found abnormalities in 71 per cent of the cases, some of which were epileptic in character. The temporal regions were not mentioned specifically, but 5-6 cycle per second rhythms from the central and frontal regions were noted. Hill and Watterson (1942) found abnormal electroencephalograms in 48 per cent of 151 "psychopathic personalities."[31] There was a much higher incidence (65 per cent) of abnormal tracings from the 66 "aggressive psychopaths" of this group. The greater incidence of abnormalities in these cases did not appear related to familial epilepsy or to past head injuries, etc. Hill (1944) subsequently

analyzed 80 abnormal electroencephalograms of "aggressive psychopaths" as regards the localization of the abnormality.[12] In 59 (74 per cent) there was the presence of bilateral 4-6 per second activity in the postcentral regions. There appeared to be two foci for this activity; one in the "high parietal" area, the other, less common, in *"the posterior temporal regions."**

In their paper of 1942 Hill and Watterson had speculated that "in view of the similarity between the aggressive behaviour of psychopaths and the normal bad-temper response to frustration in young children on the one hand, and the similarity between the E.E.G.'s of aggressive psychopaths and those of young children on the other, the suggestion that the abnormality in the E.E.G.'s in these cases is produced by a failure of development in the central nervous system is very tempting." For an elaboration on this hypothesis, as well as for a further study of temporal lobe abnormalities and their relation to distinctive psychiatric states, one is referred to a recent paper by Rey, Pond, and Evans.[39]

Simons and Diethelm found abnormal electroencephalograms in 53 per cent of 69 "psychopathic" personalities.[44] The majority of records showed an unusual amount of 5-7 per second activity in the frontal and parietal regions.

The author has been impressed that in instances where there are recurring bursts of rhythmic activity of about 6 per second (the so-called theta rhythm of Walter[50]) in adults, the waves commonly reach a maximum amplitude in the midline frontal region.† There is some indication that these rhythms have to do with pacemakers in the more primitive systems, but this remains for the future to determine.

"Mental activity." In 1937 Laugier and Liberson remarked upon a rhythm of the alpha type that appeared in the temporal regions of some individuals, and which was unrelated to the alpha activity in the occipital area.[26] In 1948 Kennedy *et al.* reported a similar type of activity in the anterior temporal regions that appeared to be associated with mental activity (e.g. the performance of calculations, etc.)[21] They referred to this activity as the "kappa" rhythm, and indicated that it is present in about 30 per cent of the "normal" population.[22] Their inference that this activity arises in the temporal lobes is supported by Arellano's findings that the tympanic electrode will frequently record these waves in as great amplitude

* Reviewer's italics.

† "Indifferent" reference electrode over the sixth cervical vertebra. When recording with a series of "active" electrodes in the frontal region, there is a phase reversal at the midline frontal electrode.

as electrodes placed in the anterior temporal region on the scalp.[3] It remains a complete mystery, however, what the mechanism of this activity is and what relationship it may have to subcortical pacemakers. The temporal activity is generally less rhythmic, somewhat slower, and of less amplitude than the occipital alpha, and occurs independently of the latter. It may be as slow as 5 per second.[22] The author has seen one patient who showed the so-called kappa activity to a striking degree both before and after bilateral frontal lobotomy. This would indicate that this rhythm is not dependent on the prefrontal regions.

"Psychosomatic" conditions. Arellano and MacLean are in the process of studying the standard and basal electroencephalogram in a number of patients with migraine[4] and with essential hypertension.[31] In about 65 per cent of each group, activity of the type described in the previous section has been seen to occur spontaneously in the temporal regions. In some instances this activity can be enhanced by "mental activity." In the present state of knowledge these findings are chiefly of descriptive interest. Perhaps they may be correlated with the observations of Walter and Walter.[52] In a fascinating study of the effects of photic stimulation on cerebral rhythms these investigators reported that "emotional and autonomic disturbances were usually correlated with augmented response at 6-7 c./ sec. from the parieto-temporal region." With photic stimulation at 5-7 cycles per second some subjects "volunteered that they found stimulation at these frequencies particularly disagreeable, not because of any visual sensation, but rather because it produced a feeling of irritation and vague discomfort. This state was susceptible to exacerbation by additional affective stress, which also augmented the response in the theta band."

Sleep. Liberson[27] and Brazier[5] have made extensive studies to determine the localization of various potentials occurring during sleep. Brazier found no characteristic potentials localized to the basal regions. Liberson encountered a temporal localization "only exceptionally."

The author and co-workers have studied the basal electroencephalogram during natural and induced sleep.[21] The "waking" electroencephalogram characteristically shows low voltage, random activity with frequencies in the alpha and beta range. It has been noted that there is little on visual inspection to distinguish this type of record from the one obtained in early sleep.[30] The use of the automatic analyzer, however, shows a shift from the higher to the slower frequencies with the onset of sleep. As sleep becomes deeper, low voltage slow activity may be visualized in the basal electroencephalogram. When sleep is induced by barbiturates, the early appearing

rhythmic low voltage 20-24 per second activity seems to be present simultaneously at the base and at the scalp. Whenever rhythmic 10-14 per second activity can be detected in the basal electroencephalogram, there are indications that this is the distant effect (volume conductor spread) of the simultaneous large potentials generated in the scalp regions or elsewhere. Occasionally one sees rhythmic 7 per second activity recorded with highest voltage from one or the other tympanic electrode.

Penfield and Erickson have suggested that dreaming may be a function of the temporal lobes.[26] In the light of this it is an interesting, though possibly not significant, observation that there is superficially little to differentiate the waking electroencephalogram of the basal temporal regions from that obtained in early sleep.

Miscellaneous observations. Arellano and MacLean have been interested in what effect various drugs and physical stimuli that act on autonomically controlled systems would have on the basal electroencephalogram.[4] As far as they have been able to determine, adrenalin, ergotamine, mecholyl, nitroglycerine, ocular or carotid pressure, and the cold pressor test, produce no changes in the electroencephalogram detectable by visual inspection.[4] In the last instance, the subjective interpretation of no change in the electroencephalogram was borne out by automatic analysis.

Comment

Many of the electroencephalographic findings summarized in this review, when taken together with clinical observations and animal experimentation,* make it increasingly clear that the temporal lobes are fundamentally concerned in the experiencing and expression of affect, as well as in the elaboration of visceral and psychical activity associated with affective states. Perhaps there is no other clinical entity that promises to shed more light on the functions of these parts of the brain in man than psychomotor epilepsy.

The evidence for believing that the primitive forebrain is basic to emotional mechanisms has been reviewed elsewhere.[20, 22, 25] That part of the primitive forebrain included in the hippocampal formation (hippocampus, amygdala, hippocampal and dentate gyri) lies in the mesial and basal parts of the temporal lobes. This region is strongly connected to the hypothalamus and other lower centers involved in emotional expression. Of particular interest is the observation that this part of the brain may be an association

* The reader may refer particularly to the experiments of Klüver and Bucy, where bilateral temporal lobectomy produced tameness in formerly wild and intractable monkeys, as well as "oral" tendencies, bizarre sexual behavior, etc.[24]

area for every form of internal and external perception, and possibly provides a mechanism for integrating and affectively experiencing impressions from the mouth, nose, eye, ear, body wall, viscera, and sex organs. Moreover, the cytoarchitecture of this region is so primitive as to suggest it could deal with information only in a crude way, perhaps being more capable of integration than differentiation, and thereby accounting for the paucity, as well as the often unpredictable overlapping, of affective reactions. Some analogies suggest that the hippocampal formation may be to the emotions what the cerebellum is to the locomotor system.

Still shrouded in mystery is what direct connections, if any, the greater parts of the temporal lobes have with the thalamus. Both clinical and animal electroencephalography suggest that this expanse of cortex is not without the influence of subcortical pacemakers. Some physiological observations of Jasper's indicate there are connections between the reticular system of the thalamus and the "temporo-parietal" region.[18] It has been suggested that the amygdala may provide an extrathalamic "clocking" mechanism for the temporal areas.[29]

Clinical electroencephalography will doubtless continue to throw light on many of the foregoing problems. Walter, however, has emphasized that limited information can be obtained by visual inspection alone of the electroencephalogram.[51] The work being done in his laboratory in England on rhythmic sensory stimulation and the automatic analysis of the underlying cerebral rhythms[52] strikes one as being among the most forward-looking in electroencephalography today.

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EVENTS

TOXICOLOGY SEMINAR

February 23, 1950

INDUSTRIAL TOXICOLOGY IN MISCELLANEOUS OCCUPATIONS. By Warren A. Cook, Director of the Division of Industrial Hygiene and Engineering, Zurich General Accident and Liability Insurance Co., Ltd.

The speaker gave intriguing examples of the Sherlock Holmes type of research that industrial hygienists perform. Two points of great importance to clinicians were stressed as follows: (i) The occurrence of occupational toxicities in vocations where least expected behooves the internist to be on guard. Cases cited were those of mercury poisoning in agricultural workers and in bowling ball balancers. (ii) The speaker emphasized the fact that figures for the maximum concentration of a toxic agent which the worker can tolerate for a given period without untoward effect are based on the study of persons with normal physiological processes. A sub-clinical pathological condition may render a man much more prone to toxic reaction than a healthy worker. Fatal cases of organic chloride poisoning were reported in patients with previously undetected, decreased hepatic function under conditions wherein other workers showed no toxic signs.

HENRY STUDE, JR.

PHARMACOLOGY SEMINAR

March 2, 1950

DIMENSIONS OF METABOLIC PROBLEMS. By Dwight J. Ingle, Director of Pharmacology and Endocrinology, The Upjohn Company, Kalamazoo, Michigan.

The term "dimensions" was defined as those independent variables and secondary effects in experimental procedures which can significantly alter results obtained, thereby leading to misinterpretation of data. These variables include such factors as time, temperature, species, strain, rate of administration, diet, etc. For example, in studies of steroid endocrinology, effects on other endocrine organs may obscure a hormone's primary action. Although control of these variables is exceedingly difficult, the speaker emphasized that the isolation and control of these dimensions has proved imperative in any attempt to discover the primary action of hormones.

HENRY STUDE, JR.

YALE MEDICAL SOCIETY

March 8, 1950

EFFECT OF INCREASED INTRACRANIAL PRESSURE ON THE PULMONARY CIRCULATION. By William Harrison, Jr. and A. A. Liebow.

The common association of increased intracranial pressure with acute pulmonary edema is well known; the purpose of these experiments was to

study pressure changes in the pulmonary circulation of 27 dogs when intracranial pressure was increased. Pressures were measured in the pulmonary artery, left atrium, femoral artery, and femoral vein. Intracranial pressure was increased by expanding a subdural bag, or by forcing Tyrode's solution under pressure into the cisterna magna through a needle or around the cerebrum through a trephine hole.

In general, when the intracranial pressure was increased, systemic arterial pressure rose first with a slight pressure rise in the left atrium and pulmonary artery. Bradycardia appeared at intracranial pressures approaching the normal diastolic level of the systemic arterial system; the bradycardia was followed by a more pronounced rise in left atrial and pulmonary arterial pressures. When apnea occurred, atropine was given, resulting in tachycardia and more normal pressures. At necropsy it was found that approximately one dog in five had developed pulmonary edema, the criterion being a lung weight greater than 1.2% of body weight. It was also noted that all of the dogs with pulmonary edema had had mean left arterial pressures above 20 cm. of water, but in six dogs which showed no pulmonary edema by weight the left arterial pressure was similarly elevated.

K. G. B.

Description of Toxin in Toxoplasmosis. By David Weinman, II. (For complete text see The Yale Journal of Biology and Medicine, 1950, *22*, 323.)

The Release of Vasoconstriction by Vasodilator Drugs and Sympathetic Nerve Block. By Lawrence G. Crowley.

Six normal young adults and four hospital patients with unilateral peripheral vascular disease (the contralateral extremity serving as a control), were utilized as subjects in studying the variations in blood flow induced by the injection of nicotinic acid, papaverine or priscoline or by sympathetic nerve blocks. Blood flow was determined in three ways: (1) by recording skin temperature changes at a constant room temperature, (2) by plethysmographic readings, (3) by determining pulse volume.

Little or no change in blood flow was noted with nicotinic acid or papaverine, while priscoline was effective in elevating blood flow consistently in the normal subjects and irregularly in the patients with peripheral vascular disease. Sympathetic nerve block increased the blood flow to a greater extent than did priscoline, its effectiveness being localized to the area of nerve distribution. It was concluded that priscoline may afford some relief in vasospastic diseases but is of no value in inflammatory or degenerative vascular lesions. Its use is contraindicated in cardiac disease. In high dosage, it may cause postural hypotension.

In view of the fact that the methods used measured blood flow to the skin and subcutaneous tissues and not necessarily to deeper structures, further experiments are being carried out to measure the rate of disappearance of radioactive sodium injected intramuscularly. All these studies have been carried out on limbs at rest, and it is planned to study changes in flow during exercise on a treadmill.

V. L. S.

A Salt-wasting Syndrome Associated with Cerebral Disease. By Louis G. Welt, Ethan A. H. Sims, Jack Orloff, James W. Needham, and John P. Peters.

Following a brief review of experiments and observations indicating that cerebral lesions, notably hypothalamic, may be accompanied by disturbances of electrolyte balance, three cases from the New Haven Hospital records were presented in which similar phenomena occurred. The diagnoses were acute encephalitis, cerebrovascular accident, and bulbar poliomyelitis, respectively. Each patient exhibited a negative balance of sodium and chloride in the face of depressed concentration of these ions in the serum. This salt-wasting phenomenon appeared to recede in two patients and was proved to have disappeared in the other patient with clinical recovery from the primary central nervous system disease. The authors speculated that this effect may have been mediated through interference with neural connections to the anterior pituitary affecting ACTH production, or through yet unknown direct neural control of the renal tubules.

W. P. McN.

ZOOLOGICAL JOURNAL CLUB

March 9, 1950

Heterosis. By Theodosious Dobzahnsky, Professor of Zoology, Columbia University.

When individuals of different genetic races are crossed, the offspring may show increased vitality; this phenomenon has been termed heterosis or hybrid vigor. Cytological examination revealed that the chromosomes of populations of *Drosophila pseudo-obscura* collected from regions of the southwestern United States were of four types (designated as A, B, C and D) characterized by the presence of inverted segments. The frequency of these types was characteristic for a given population of flies. Study of a population which was the product of interbreeding groups of A and B showed that the heterozygous AB had a higher survival value than either AA or BB. The same held when C was introduced with A or B. Thus the heterozygous individuals exhibited heterosis, being in some way favored by differential mortality between egg and adult. The infrequent type D failed to exhibit heterosis with A or C but BD had a higher survival value than BB or DD. The low survival value of the DD group appeared to indicate some deleterious effect. The persistence of D was interpreted as the preservation of an unfavorable genetic influence which favored adaptation of the population as a whole by maintaining its flexibility. AA individuals from one region were combined with BB individuals from another region, the object being elucidation of the genetic mechanism of heterosis. The resultant AB group failed to exhibit heterosis. The speaker interpreted these data as indicating that the phenomenon could be attributed to the action of balanced polygenes. Chromosomes of a given type from different regions were considered morphologically alike but genetically different,

having evolved in a manner best suited to their environments and in such a way that the heterozygous condition resulted in more favorable gene interaction.

R. R., JR.

March 22, 1950

SURGERY ON THE EMBRYONIC BRAIN IN RELATION TO PROBLEMS OF BEHAVIOR. By S. R. Detwiler, Department of Anatomy, College of Physicians and Surgeons, Columbia University, New York.

By extirpation, grafting, and quantitative evaluation of certain behavior patterns the speaker sought to correlate structural alterations of the brain with function. Operations were performed on the early embryos of *Amblystoma punctatum,* the yellow-spotted salamander. Operated motile larvae were placed in a calibrated circular dish and subjected to a constant number of tactile stimuli over a constant period, total distance travelled and response to individual stimuli being noted. Individuals in which the forebrain had been removed were capable of integrated behavior although response was slow. The receptor apparatus of the lateral line system was sufficiently sensitive to enable these animals to seize moving food although they lacked eyes and nasal structures. Those animals in which the midbrain had been removed and replaced by a segment of spinal cord at first exhibited normal swimming responses. In later stages, however, there was a marked decrease in locomotor ability. These results were interpreted to indicate that the early spinal mechanism is autonomous but requires the presence of the midbrain in later stages. When the brain was reversed end-to-end, subsequent behavior and structure of the brain were almost normal. Locomotor responses greater than normal could be elicited in which a second midbrain had been substituted for the hindbrain. This hyperactivity was attributed by the speaker to the lack of a regulatory mechanism associated with the hindbrain. Previous neurological study indicates that either the dorsal tegmental nucleus or the ears might serve as regulators of activity. Since earless, otherwise normal animals failed to exhibit hyperactivity, the hypothesis of a regulatory role for the dorsal tegmental nucleus was to some extent supported.

R. R., JR.

NU SIGMA NU ANNUAL LECTURE

April 21, 1950

ACTH AND CORTISONE. By Dr. Philip S. Hench, Mayo Clinic, Rochester, Minnesota.

Following observation twenty years ago that jaundice and pregnancy produced temporary ameliorations of rheumatoid arthritis, a search was begun for a "Compound X" common to these conditions which might be responsible for these remissions. Various adrenocortical products were tested without success, until Compound E, renamed cortisone, became available in sufficient quantities in September, 1948, for clinical trial on a small

number of patients. ACTH was also used clinically. [Dosage ranged from 25 to 300 mg. per day of cortisone or 25 to 100 mg. per day of ACTH, the optimum being 100 mg. of cortisone and slightly less than 100 mg. of ACTH. The length of administration varied from less than a week to six months.]

The results, both with cortisone and ACTH, were dramatic, producing subjective relief in a few days and objective improvement in a somewhat longer time. The improvement in the majority of patients was categorized as very marked or marked; in none was there no improvement. The induced remissions lasted at the minimum one day to a maximum in a few cases of 14 months after cessation of the hormone. The degree of return of symptoms also varied from a rebound relapse with exaggeration to partial return of pain and swelling. The question of the length and degree of the induced remission is complicated by the frequency of spontaneous remissions in the disease.

Side effects were none or mild in 17 of 23 patients. The principal of these effects were salt and water retention with edema, mild hypopotassemic hypochloremic alkalosis, rounding of the face, acne, mild hirsutism, changes in the libido and potentia, amenorrhea, skin striae, reduction of carbohydrate tolerance, and swings of mood. Small dosages, interrupted course methods of administration, salt restriction, and, in certain instances, testosterone (for nitrogen deficit) and estrogens were advocated to control the side effects. Men were noted to be less prone to side effects than women, and pubertal and menopausal women were found to be the most sensitive.

A series of other adrenocortical products tested on a few patients were without effect except for Compound F and an oral cortical extract, both of which are rarer and neither superior to cortisone or ACTH. Cortisone exhibited beneficial effects on the course of acute rheumatic fever, disseminated lupus erythematosus, and psoriasis with psoriatic arthritis. It produced clinical improvement in two cases of tuberculous arthritis without changing the bacteriology of the lesion—that is, it appeared to affect only the hypersensitivity component of the pathologic picture.

These results do not answer the question of the theoretical relationship of the adrenal cortex to these diseases—whether the disease state is one of relatively insufficient production, one of abnormally high destruction, or one of abnormal demand of hormone. The author emphasizes that these are preliminary experiments in clinical physiology rather than therapy.

W. P. McN.

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BOOK REVIEWS

ONE HALF THE PEOPLE: DOCTORS AND THE CRISIS OF WORLD HEALTH. By Charles Morrow Wilson. New York, William Sloane Associates, Inc., 1949. 315 pp. $4.00.

Mr. Wilson has traveled a great deal and in this, his nineteenth book in forty-five years of life, he presents vividly the far-flung problems of world health.

The plan of the volume is like an adventure story on a radio "cereal" program. It starts with a bird's-eye view of world-wide problems in disease and starvation. It tells of the struggles and efforts of native doctors in West Africa and in an isolated Indian tribe in Mexico. It leaps back to the health problems of the United States, the scandal of patent medicines, and the issue of voluntary versus compulsory health insurance to finance medical care. Then comes a snatch of medical history to give some appreciation of the background of modern bacteriology and public health, stressing the contributions from many different nations. Then back to Africa for more of the trials of native medicine, and over to Madison County, Arkansas, where the doctor's task has its primitive features. A chapter follows on Central and South America, reminding us of the historic fight of Reed and others less famed against mosquito-borne disease.

In "Sickness and Health Around the Equator" the story goes into high gear—the tale of human wastage and dilapidation from tropical disease. We read of malnutrition, sleeping sickness, Chagas' disease, poliomyelitis, tuberculosis, cholera, schistosomiasis, and malaria. Then we take a look at health service organization under Soviet communism, its regimentation and its accomplishments. Finally comes the "wind-up" with a tribute to the early efforts of the World Health Organization and a look ahead with caution: if we take a world-wide view and organize to promote the health of all people, mankind may survive. Otherwise, perhaps Malthus was right, and man shall some day perish.

The author's great productivity is to be noted, for the abundance of errors in the text suggests that the book was written in haste. Despite the numerous medical and public health fallacies, however, the basic message of the volume is sound. It is nowhere clearly stated, but one suspects that the author is trying to say that we live in One World and, if we are all to flourish, the medical knowledge of our great centers must be brought to bear on the lives of all men, whether in a rural county of the United States, an African jungle, a Carribean island, or a Russian village. To do this requires vast social organization and international co-operation and planning. There can be little disagreement with this thesis.

One Half the People is interesting reading and may tell the message of world health needs to the average citizen more effectively than the technical bulletins of the World Health Organization in Geneva. Many popular health writers, however, have learned to double check their stories with

competent experts so that accuracy and balance are not sacrificed to dramatization. If this had been done, one could recommend without misgivings that the book would be worthy of wide circulation.

MILTON I. ROEMER

PHYSIOLOGY IN DISEASES OF THE HEART AND LUNGS. Harvard University Monograph in Medicine and Public Health, Number 10. By Mark D. Altschule. Cambridge, Harvard University Press, 1949. xv + 368 pp. $5.00.

In acceding to the request of his clinical students at Harvard for this book, the author has placed in his debt students (and teachers) everywhere. The book is for the knowledgeable reader, not the type seeking information on the normal level of this or that element in the blood. It considers chronic cardiac decompensation at length, followed by excellent discussions of the physiological backgrounds of acute pulmonary edema, angina pectoris and myocardial infarction, cardiac arrhythmias, pericarditis, cardiac defects, pulmonary fibrosis, emphysema, bronchial asthma, pleural effusion, pneumothorax, and pneumonia. It is a masterpiece of epitome, but in its abundant bibliography it is a guide to the exploration of volumes containing the basic data. Thus, for a three-page discussion of circulation time there appear six and one-half pages of references. In its attitude, however, this little volume is more than a mere *Index Physiologicus*. It has viewed the subject matter with a critical eye, like the worker who "stated that bile pigment is not found in edema fluids, although his data show otherwise" (p. 129). An outstanding example of the clarity of the author's thought and expression may be found in his summary of "cardiac asthma." Bibliographically, the work has been excellently done. It would be picayune to point out the few errors disclosed, as in the references to Posner, or Telemann (p. 121). This little volume will do much to dispel the obscuration produced by those who, in the author's words, "like the squid, beclouds the issue with jets of ink as he proceeds erratically backwards."

A. A. L.

BIOLOGIE DER GOETHEZEIT. By Adolph Meyer-Abich. Waltham, Mass., The Chronica Botanica Co., 1949. 303 pp. $5.50.

Naturalists have not agreed as to the significance and value of Goethe's contribution to natural science. His "Farbenlehre" has been severely criticized for obvious reasons. His undisputed biological contributions, the concept and name of morphology, the theory of metamorphosis, the intermaxillary bone, and the ideas on the interrelationships of all living forms have been minimized by some, but have been hailed by exuberant followers of Darwin, eager to show that Goethe was an early exponent of the theory of evolution and their true *poeta laureatus*. We know, however, that Goethe's ideas in matters of constancy of the species remained oscillating and undecided, that his famous metamorphoses around a fictitious or real "archetype" were idealistic-morphological abstractions rather than concrete

genetic modifications in time. Goethe's true position, the writer of this review feels, might have been recognized more clearly if in the controversy the personal element in Goethe's character had not been neglected unduly. The wholeness of Goethe's personality, so averse to an exclusively centrifugal mode of living, but so wholly given to a combination of high-hearted neo-classic idealism and romantic-sensualistic experience, was not exactly fertile ground for the growth of ideologies mathematical rather than qualitative in nature. Art and science were to him mutually beneficial activities, but in times of stress, when "Weltschmerz" almost overwhelmed him, Goethe would seek consolation through the medium of art rather than science; he has said so plainly in his famous "Marienbader Elegie."

Ernst Cassirer, well remembered by friends and colleagues at this University, analyzed Goethe's natural science with the philosopher's tools, pointing out important differences between the mathematical approach of Newton and Kant and Goethe's method which has to do with individual, qualitative phenomena and their ideal abstractions, the archetypes. Goethe surely never intended to sacrifice their symbolic value for the mathematical transcriptions and uni-directional series of mechanistic natural science. Meyer-Abich's book (in German), approaching Goethe's natural science from the historical-philosophical point of view, makes this more explicit. He discusses in detail the main differences which exist between ancient and modern natural science, and between the biological concepts of Goethe and his contemporaries, on the one hand, and the majority of present-day biologists, on the other hand. Goethe's idea of nature is essentially a dynamic renaissance of Platonic-Aristotelian principles in modern *holistic* form. Although at the present time, modern natural science is essentially a mechanistic discipline, basically mathematical, and influenced by certain principles (such as dynamic change and infinite development), it will assume a character increasingly holistic. Goethe in his biology already has fulfilled this promise within the limitations of his time; it is classical-holistic in its theoretical premises, but modern in its empirical approach.

In addition to a general introduction, biographical data with portraits, and a section on Goethe's law of compensation, the bulk of the volume consists of selected morphological writings by Goethe (omitting the readily available Plant Metamorphosis and the article on the intermaxillary bone) and of papers by his contemporaries, namely, Forster (A view into the whole of nature); A. v. Humboldt (The vital force or the Rhodian genius); Oken (Development of the scientific systematics of animals); C. G. Carus (Which are the prerequisites for a future treatment of the natural sciences?); v. Baer (Which concept of living nature is the right one?); and Joh. Müller (Of the need of physiology for a philosophical view of nature).

ROBERT BLOCH

MICROBIOLOGY. By Florence C. Kelley and K. Eileen Hite. New York, Appleton-Century-Crofts Inc., 1949. xiii + 592 pp. $6.50.

The authors present a survey of the major groups of microorganisms

with special emphasis on those of medical and industrial importance. Since the work is intended for elementary students, they have wisely included extensive sections on techniques of cultivation and classification, the various tools of microbiology, chemotherapy, and bacteriostasis. A reasonable balance is maintained between the structural and functional aspects of classification. The printing and most of the illustrations are excellent and the format attractive.

In view of the present widespread interest in the intermediate metabolism of carbohydrates and proteins, the coverage of these topics seems unduly brief and antiquated. The general microbiologist may also feel that too great stress is laid upon the epidemiological aspects of the pathogenic organisms. The treatment of the Algae and of the Fungi, with the exception of the human pathogens, is very scanty and outdated. Photosynthesis and chemosynthesis are discussed in the most superficial terms. In brief, the reviewer feels that the title "Microbiology" is too inclusive for a book which is essentially only a text in elementary bacteriology.

V. M. C., JR.

BIOLOGICAL ACTIONS OF SEX HORMONES. By Harold Burrows. New York, Cambridge University Press, 1949. 615 pp. $8.50.

Considerable new material has been added to this second edition of Harold Burrow's review of the biological actions of the sex hormones. The present edition and its predecessor contain an unequalled, compact, and complete storehouse of detailed information, particularly useful to the experimental biologist. The work represents a real achievement. As such, an enumeration of a few picayune errors and omissions seems unwarranted. While some readers might object to the fact that many clinical aspects of endocrine disorders in man are not adequately treated, it must be recognized that only with a background in experimental biology as presented by the author can human disorders be adequately and completely interpreted.

The reviewer found the book to be readable and well printed. It contains an excellent index.

W. W. E.

CURRENT THERAPY 1950. Edited by Howard F. Conn. Philadelphia, W. B. Saunders Company, 1950. xxxi + 736 pp. $10.00.

Like its predecessor, CURRENT THERAPY 1949, this volume presents articles on each disease, written by a consultant with wide experience in that field. The diseases are grouped into fifteen sections, i.e., diseases of the locomotor system, obstetric and gynecologic conditions, diseases of the skin, etc. Only therapy is included in the volume which is certainly consistent with its title, although its value to students and clinicians might be increased were it to include differential diagnostic points in the appropriate articles. In some instances where significant differences of practice exist in regard to a particular condition, two or more procedures in use by them are cited by the several authors. Controversial regimes and the use of new

drugs, for which sufficient clinical experience has not been obtained, are not included. The work is conveniently arranged and efficiently indexed for handy use by the busy practitioner.

W. F. S.

THE NATURE OF NATURAL HISTORY. By Marston Bates. New York, Charles Scribner's Sons, 1950. 309 pp. $3.50.

As author, traveler, and scientist, Dr. Bates is well qualified to expand "the approach of science to the living world" for laymen and specialist alike. His book has the personal quality of a collection of essays but contains considerable information from the fields of biological concepts and the allied sciences, colored with biographical sketches and humor. As one might expect from the title, he occasionally teeters on the edge of philosophical whirlpools but, in general, confines his discussion more closely to the questions than to their possible answers. Perhaps the most readable part of the book deals with biological interrelationships. Here he suggests that his purpose is the further application of the methods of biological relationships to human achievement outside of science. This purpose is overshadowed, however, by a more subtle and important achievement—the conveyance of his own curiosity and enthusiasm. Thus, *The Nature of Natural History* is not a report of new scientific work but rather contributes to the enjoyment of anyone interested in science or scientists.

O. L. K.

CHARLES DARWIN THE NATURALIST AS A CULTURAL FORCE. By Paul B. Sears. New York, Charles Scribner's Sons, 1950. ix + 124 pp. $2.00.

In reading Dr. Sears' concise but nonetheless informative evaluation of Charles Darwin and the theory of evolution one senses that the author is attempting more than a cursory review of the subject matter. Yet it is quite difficult to derive a consistent argument with valid conclusions from his book. Dr. Sears, realizing that knowledge without morality can wreak destruction on mankind, makes a valiant effort to establish an objective basis for moral judgment. There must be a universal source of agreement and an understanding of brotherhood; this, he feels, can come from the fact of the common descent of man as proclaimed in the theory of evolution and, to a somewhat limited extent, from science. Even religion is to "square itself at the start with the physical and biological verities." Yet, science can give no objective foundation to religion for "religion deals with much that is beyond the present reach of science." Herein is a dilemma which is not resolved.

Perhaps if we examine ethical behavior on a broader basis, we may still hope to discover the universal principle Dr. Sears urgently demands. He tells us that conduct is based upon man's conception of the kind of universe of which he is a part. Further, every human culture has its own conception of the universe, and its standards of "enlightened ethical behavior" are based upon that concept. Thus it becomes necessary to insist that each culture have the same basic concept of the universe.

The only hope is education, yet the limitations placed on this solution are severe. The author feels that the rightful function of education is to fit the young "to participate in their culture and to preserve it"; social change must come from the adult community, not the schools. In addition, each culture is "to have considerable respect for the past and its achievements, to rely on scrutiny and selection at least as fully as on experiment. . . ." Under such restrictions education can never transcend the tight boundaries of individual cultural groups in anything but science, which we previously found inadequate to establish universal moral judgments.

It would appear then that Dr. Sears is left with the theory of evolution as his sole universal principle. He answers the neo-Darwinian school by citing mutual aid as evidence against competition and struggle. However, mutual aid is but an empirical fact which would seem to satisfy antithetic hypotheses. Thomas Hobbes' idea of man under natural law is not contradicted by the fact of mutual aid. Nietzsche is summarily dismissed, maybe rightly so, but his belief in the struggle against nature and the will for power cannot be ignored when considering the philosophic significance of the theory of evolution.

Possibly much of the confusion arises from the oversimplification which brevity necessitates. Dr. Lecomte du Noüy has observed that the "scale of observation" colors any conclusions obtained. Dr. Sears passes from the philosophic implications of the theory of evolution to the effect of the theory on democratic schools, etc., with but brief regard of the different conditions inherent in such diverse situations. Had his perspective been as constant as, for example, the view of the universe taken by George Stewart in *Man, An Autobiography,* the argument would have been more lucid. Nonetheless, Dr. Sears surveys a very difficult subject in a brief and provocative manner, and points up many relevant and interesting facts concerning Charles Darwin and the theory of evolution.

K. G. B.

HISTOLOGY. By Arthur W. Ham. Philadelphia, J. B. Lippincott Company, 1950. xix + 756 pp. $10.00.

A book in which an effort has actually been made to present a subject to beginning medical students as clearly and interestingly as possible has been published in the field of histology. This stated goal of Dr. Ham's has been thoroughly achieved, for the book serves not only as a fine histology text, but as an excellent introduction to endocrinology, cytology (in the presentation of staining techniques), and many aspects of physiology. Dr. Ham's claim for its usefulness to graduates of medicine may perhaps be questioned, however, since his treatment of topics is of necessity on a plane too broad to be suited to few other than freshman students.

The outstanding feature of the book is the author's ability at clear expression free from the usual textbook faults of monotony in style and sickening repetition. The sections on bone and tooth formation should be

especially noted for their clear explanation of topics not always well treated in other texts.

The organization of material is to be commended on several counts. Knowledge from other fields, along with many pertinent clinical facts, is skilfully and extensively woven into the histological description instead of being artificially consigned to separate sections or omitted altogether. An outstanding example is the section on skin grafting and regeneration. Interest is sustained and the student is given a wider view through the numerous short accounts of the research leading up to a modern concept. And finally, on a materialistic level, the student will undoubtedly appreciate Dr. Ham's recognition of some of the difficulties encountered in the laboratory. There is a section at the beginning of the book on common artifacts and one finds remarks throughout on staining problems which account for some structures being seen with difficulty or not at all under certain stains.

The format, paper, print size, and half-tones are all excellent, though the four-color plates are not especially noteworthy. Indeed, one color plate (showing endochondral bone formation) with an added tissue paper sheet for its legend seems entirely superfluous and extravagant. It is very unfortunate if this plate contributed materially to the book's being considerably more expensive than other histology texts. It is to be hoped that a large circulation and economies in printing will allow the price of this text to be reduced to that of its competitors. The average medical student, I believe, can better appreciate a trend toward more readable texts if it does not simultaneously mean a trend toward further drainage of his wallet.

R. G.